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for doctors and their patients

e Official Journal of the NORTH CAROLINA MEDICAL SOCIETY January 1984, Volume 45, No. 1

Otto Warburg 1883-1970

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SCIENTIFIC ARTICLE

Outpatient Adolescent Gynecologic Disorders

Joseph F. Russo, M.D.

THERE is increasing interest in the gynecologic disorders of adolescents. Early maturation and increased sexual activity have resulted in a need for medical consultation and treatment. One thousand sixty-four teenage females between the ages of 11 and 17 years made 3,540 visits to the Adolescent Gynecology Clinic of the UMD-New Jersey Medical School during a six-year period, one in 10 of the total gynecologic visits. The practitioner might then expect to see a young patient with a gynecologic problem approximately twice a day.

The types of gynecologic disorders with which adolescent patients presented on their visit were analyzed and grouped into broad categories. The goal was to document the relative frequency of various disorders. No attempt was made to detail the diagnostic and therapeutic methods employed since these have already been described.[1] The results highlight the gynecologic problems that are likely to be encountered in an office practice and point out the need for more attention to this specialized area of gynecologic care.

The seven types of gynecologic disorders in decreasing order of frequency were menstrual irregularities, genital tract infections, postabortion and postpartum referrals, lower abdominal pain, routine examinations, contraception, asymptomatic adnexal masses. The problems were similar to those of adult females. There was greater difficulty, however, in making a diagnosis and providing effective treatment. The approach of the physician and the staff to the adolescent female was different from that used with adult females because it took into account the young woman's stage of psychosocial development. No definitive diagnosis was made without a complete pelvic examination, which in some cases required a second visit. Pap smears were routinely performed. We convinced the patient of a need for a complete examination and performed it after receiving her consent.

Adolescence is a psychologic transition period between childhood and adulthood. This process does not depend on chronological age but is conditioned by pubertal growth and the societal environment. Three substages of psychosocial development during adolescence have been identified. Each affects and is affected by the adolescent's self-image and relationship with her family and her peer group.

During early adolescence the female understands little about how her body works, but is greatly concerned with her body image. It has been our experience that the early adolescent female usually comes with her mother and needs her throughout the visit. Treatment and compliance depended on both.

At mid-adolescence most physical development is complete, but knowledge of bodily functions is often incomplete. Furthermore, the young woman's behavior is affected by the actions of her peers. Idealism and fantasy often dominate her thinking. The mid-adolescent female usually does not want her mother present during the medical interview and physical examination. Our approach has been to persuade the mother of her daughter's need to have a confidential relationship with her physician. Treatment and compliance depended on the young woman's understanding and willingness.

By late adolescence the young woman understands how her body works and is more realistic. Therefore, she is an easier patient with whom to deal and is not usually seen in our adolescent clinic.

One-fourth of the patients presented with a menstrual irregularity. The variations in adolescent bleeding pattern were many and it was difficult at times to identify the difference between physiologic normalcy and pathology. The practitioner must have a thorough understanding of the normal progression of physical changes associated with puberty. The diagnosis of constitutional amenorrhea, for example, was based on physical signs that the appropriate stage of pubertal development had not been reached. More than half of the young women were pregnant. The younger the teen, the less likely she or her mother were aware of this possibility. Therefore, patients were routinely screened for pregnancy prior to endocrinologic evaluation. Anovulatory cycles was another common cause for a menstrual disorder. The diagnosis can be established by observing the presence of normal secondary sexual characteristics, obtaining a normal serum prolactin, and inducing withdrawal bleeding with medroxyprogesterone. It has been our experience that the earlier the age of onset of menarche, the greater the interval between menarche and ovulation. Even though pregnancy and anovulation were the most common causes of menstrual irregularities, the practitioner must be prepared to exclude other causes. The routine use of oral contraceptives to regulate menstrual cycles prior to the establishment of a diagnosis should be avoided. A detailed discussion of the diagnostic and therapeutic approach has been described previously.[2]

One-fifth of the patients had a genital tract infection. Fortunately, 93 percent involved the lower genital tract only. Even though the majority of the patients with vaginal discharges were infected with either *Candida albicans* (38%) or *Trichomonas vaginalis* (32%), 9 percent were infected with *Neisseria gonorrhoeae*. Six percent of asymptomatic patients were infected with this microorgan-

From the Department of Obstetrics and Gynecology, East Carolina University School of Medicine, Greenville 27834.

ism as well. These findings support the need to screen all patients for its presence. During the course of pubertal development prior to the onset of menses, some teenage females in response to increased estrogen levels present with a profuse vaginal discharge containing desquamated vaginal cells.

Sixteen percent of the patients presented with lower abdominal pain. One-third had primary dysmenorrhea which could be relieved with either prostaglandin synthetase inhibitors or ovarian suppression with exogenous hormones. The others were difficult diagnostic problems. No cause could be found in 17 percent. Many patients had previously been told that they had chronic salpingitis, but only 14 had findings consistent with that diagnosis. A few patients had an ovarian cystectomy based on an ultrasonic diagnosis without cure of the pain. Since functional ovarian cysts are not uncommon in this age group, surgery should be deferred unless the cysts are large, persistent, or twisted. Laparoscopic evaluation is extremely helpful in establishing a cause in both acute and chronic pain.

A significant number of patients (20%) were healthy young women who were utilizing gynecologic services for the prevention of diseases or pregnancy. One hundred and ten patients requested routine examinations of the breast and pelvis or wished to be screened for venereal disease. In general, the visit was initiated by the mother of the young teenagers (11-14 years) or by the patient when older (15-17 years). Interestingly, all these patients had normal physical and laboratory findings. The majority of younger adolescents were not sexually active even though their mothers assumed that they were. It has been our impression that mothers were more likely to bring their young daughters to be seen if they themselves had conceived during early adolescence. One hundred and nine patients came solely for contraception. The majority of these patients (90%) chose the oral contraceptives. Over 90 percent of the postabortion and postpartum referrals left with a contraceptive method. Long term compliance (18 months), however, was poor (40%). Compliance could be improved if the mother of the younger teens were involved or with frequent office visits or phone contact with older teens. For patients seeking contraceptive advice, a specific approach was used.[3]

The impact of the increased level of sexual activity among adolescents on health care providers is evident from the data. Sixty percent of the patients came for their visit because they had a complication related to sexual activity (pregnancy, postpregnancy, infection, and contraception). These potential consequences of sexual activity should be explained to those young women who are considering become sexually active.

The data from this analysis point to the wide range of disorders that may affect adolescent females. In order to be effective the physician and staff must have an understanding of developmental psychology, physical growth and development, and gynecologic disorders. To this end, the author believes that the establishment of units for the specialized care of female adolescents with gynecologic disorders should be encouraged.

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SCIENTIFIC ARTICLE

Hypothalamic Releasing Factors for ACTH and Growth Hormone: Two Newly Discovered Peptides with a Promising Future in Clinical Medicine

David A. Ontjes, M.D., and Louis E. Underwood, M.D.

THE long-suspected connection between the brain and the endocrine system and the search for hypothalamic hormones was begun nearly forty years ago, when Geoffrey Harris of Cambridge University reviewed the available evidence and came to a compelling conclusion:

> There is much experimental and clinical evidence that the hypothalamus is functionally linked with anterior pituitary activity. The most direct route by which this influence might be exerted is by means of the nerve fibers or blood vessels of the hypophysial stalk. It seems possible to eliminate the nerve fibers from participation — however the portal vessels of the stalk, unlike the nerve fibers may undergo repair following stalk section, and so re-establish humoral transmission of stimuli.[1]

Guided by the concept that humoral messengers might reach the pituitary via the hypophyseal portal vessels, investigators began the search for hypothalamic substances capable of causing the release of specific pituitary hormones. The isolation and elucidation of these releasing factors was hampered for many years by lack of precise and sensitive assays, and by the extremely small quantities of the factors actually present in hypothalamic tissue. The first major breakthrough occurred in 1970 when the laboratories of Guillemin and Schally first isolated and characterized the structure of thyrotropin-releasing hormone or TRH. One of the most exciting achievements in medicine in the past decade has been the elucidation of the structure and physiological characteristics of releasing or inhibiting factors for each of the classical hormones of the anterior pituitary. The names of the known factors and some of their major effects are summarized in table 1.

In this article we will review the current knowledge relating to the two most recently discovered factors, corticotropin-releasing factor, or CRF, and growth hormone-releasing factor, or GRF. Both have been isolated and characterized only within the past two years. Information on both is accumulating so rapidly that a lengthy review would be inappropriate and quickly out of date. We hope, however, to provide readers with a short summary of important initial observations and a tentative assessment of the potential role of these hormones in clinical diagnosis and therapy.

From the Departments of Medicine and Pediatrics, University of North Carolina School of Medicine, Chapel Hill 27514.

Corticotropin-Releasing Factor (CRF)

More than 25 years ago, extracts of hypothalamus were found to stimulate ACTH release from pituitary tissues. Over the intervening years, a number of substances with corticotropin-releasing activity have been identified. Among these are vasopressin, norepinephrine, angiotensin II, and fragments of large proteins such as hemoglobin or myelin. None of these substances has met the criteria necessary to be considered a primary humoral regulator of ACTH secretion.[2, 3] Interestingly, the substance now widely accepted as the physiological CRF was isolated as a by-product of a search for a quite different releasing factor.

Structure of Growth Hormone-Releasing Factor (GRF) Isolated from Human Pancreatic Tumor

H - Tyr - Ala - Asp - Ala - Ile - Phe - Tyr - Asa - Ser - Tyr - Arg - Lys - Val - Leu - Gly - Gln - Leu - Ser - Ala - Arg - Lys - Leu - Leu - Gln - Asp - Ile - Met - Ser - Arg - Gln - Gln - Gly - Glu - Ser - Asn - Gln - Glu - Arg - Gly - Ala - Arg - Ala - Arg - Leu - NH_2

Structure of Corticotropin Releasing Hormone Isolated from Sheep Hypothalamic Tissue

H - Ser - Gln - Glu - Pro - Pro - Ile - Ser - Leu - Asp - Leu - Thr - Phe - His - Leu - Leu - Arg - Glu - Val - Leu - Glu - Met - Thr - Lys - Ala - Asp - Gln - Leu - Ala - Gln - Gln - Ala - His - Ser - Asn - Arg - Lys - Leu - Leu - Asp - Ile - Ala - NH_2

Figure 1. *Primary amino acid sequences of hpGRF-44 (from Esch, F. S., et al, reference 17) and ovine CRF (from Vale, W., et al, reference 3).*

Table 1
Hypophysiotrophic Hormones Whose Structure Is Known

Hypophysiotrophic Hormone	Structure	Described Effects on Pituitary
Thyrotropin Releasing Hormone (TRH)	Tripeptide amide	Release of TSH, Prolactin
Gonadotropin Releasing Hormone (GnRH)	Decapeptide amide	Release of LH, FSH
Prolactin Inhibiting Factor (PIF)	Dopamine	Inhibition of Prolactin release
Corticotropin Releasing Factor (CRF)	Polypeptide amide (41 amino acids)	Release of ACTH, β-LPH, Endorphins
Growth Hormone Releasing Factor (GRF)	Polypeptide (approx 44 amino acids)	Release of Growth Hormone
Somatostatin or Growth Hormone Inhibiting Factor (SRIF)	Polypeptide (14 amino acids)	Inhibition of Growth Hormone release Inhibition of TRH-stimulated TSH release

Dr. Wylie Vale and his colleagues at the Salk Institute for Biological Studies began their purification of CRF with a side fraction of 490,000 fragments of sheep hypothalamus that had been processed earlier in a successful program to isolate gonadotropin-releasing hormone. The major fraction having CRF activity turned out to be a 41 amino acid peptide amide with the sequence shown in figure 1.[3] The same laboratory quickly produced a facsimile of the native peptide using solid phase peptide synthesis, and developed a sensitive radio-immunoassay capable of measuring the peptide in biological materials. With an adequate supply of the synthetic peptide available for testing, the stage was set for rapid progress in characterizing the biological properties of this substance. Evidence to date strongly suggests that the peptide plays a central physiological role in controlling pituitary function.

Physiologic and Pharmacologic Effects of Ovine CRF. When tested for effects on rat pituitary tissues *in vitro,* synthetic ovine CRF releases equivalent quantities of both ACTH and β-endorphin or β-lipotropin. This is to be expected since both ACTH and β-endorphin are known to be products of a larger prohormone. Ovine CRF is at least 10 times more potent than any other substance known to have ACTH-releasing activity. Dose-related responses may be observed with *in vitro* concentrations of 10 pM or more,[3] while preliminary estimates of immunoassayable CRF concentrations in rat hypophyseal portal blood are in the range of 100 pM or less.[4] Human pituitary tissue responds to concentrations of ovine-CRF as low as 1 nM, suggesting that an identical or very similar peptide may be a physiologically significant CRF in man. Longer term exposure of adenohypophyseal cells to CRF leads to increased synthesis of ACTH as well as release.

The interaction of CRF with other factors that may also influence ACTH secretion is still in the early stages of investigation. Since an immediate effect of CRF on corticotropin-producing pituitary tumor cells *in vitro* is stimulation of cyclic AMP production, cyclic AMP has been proposed as a second messenger for the action of CRF, just as it has for many other peptide hormones.

Clearly, the negative feedback of glucocorticoids upon ACTH secretion will acquire new meaning when the interrelations with CRF are better understood. Thus far it is clear that glucocorticoids have a potent direct effect on the pituitary cell. Pretreatment of pituitary cells with very low (4 nM) concentrations of dexamethasone blocks the responsiveness of the cells to test doses of CRF in a noncompetitive manner. The full blocking effect of the steroid requires 4 to 8 hours to develop and does not dissipate for up to 24 hours after steroid removal.[5]

It is quite likely that in addition to direct negative effects on pituitary cells, glucocorticoids will be shown to have a negative effect on the synthesis and secretion of CRF by the hypothalamus.[2] Immediately after bilateral adrenalectomy in rats, the content of immunoreactive CRF in the median eminence of the hypothalamus drops, suggesting depletion due to rapid secretion. However, after 2 weeks immunoreactive CRF levels in the same tissue rise to supernormal levels, as if a compensatory increase in the rate of CRF synthesis has occurred.[6]

CRF as a Diagnostic and Therapeutic Agent. One of the most frequent causes of spontaneous Cushing's syndrome is hypersecretion of ACTH by a pituitary tumor, most commonly a microadenoma. Since Cushing's syndrome may also be caused by hyperfunctioning primary adrenal tumors or by the secretion of excessive quantities of ACTH-like peptides by tumors of non-pituitary origin, accurate diagnosis of the etiology of cortisol excess is essential for appropriate treatment. The differential diagnosis of Cushing's syndrome has depended on the use of one or more of the tests summarized in table 2 and reviewed elsewhere.[7] Generally, the most useful test in differentiating pituitary Cushing's disease from other causes of cortisol excess has been the so-called "low dose" dexamethasone suppression test, giving 2 mg of dexamethasone daily and measuring the effects on plasma cortisol and urinary 17-hydroxycorticosteroids. Early experience with CRF in patients with various forms of Cushing's syndrome suggests that the hormone may provide useful additional diagnostic information in some cases. Before the CRF test can be accurately evaluated, dosage regimens and normal ranges of response must be more accurately defined and standardized. It is clear at this time that both normal subjects and most subjects with pituitary ACTH excess respond to intravenous CRF with increases in plasma ACTH (peak 15-30 min) and cortisol (peak 45-60 min).[8-11] The majority of patients with ACTH-secreting pituitary adenomas show a larger than normal increment in plasma ACTH after iv doses of CRF ranging from 100 to 200 μg. A significant minority of such patients, however, show responses no greater than normal.[9, 11, 12] Very few patients with other causes of Cushing's syndrome have thus far been

Table 2
Typical Responses of Normal Subjects and Patients with Cushing's Syndrome in Response to Several Diagnostic Tests

	Dexamethasone 2 mg/day	Dexamethasone 8 mg/day	ACTH Infusion	Metyrapone	CRF Infusion
Normal Subjects					
Plasma cortisol	↓ (< 5 μg/dL)	↓ ↓	↑ (> 15 μg/dL)	→	↑ (~ 2 fold)
Urinary 17-OHCS	↓ (0-3 mg/day)	↓ ↓	↑ (2-4 fold)	↑ (2-4 fold)	↑
Plasma ACTH	↓	↓ ↓		↑	↑ (~ 2 fold)
Pituitary ACTH Excess					
Plasma cortisol	→	↓	↑ ↑	↑ ↑	↑↑ or ↑
Urinary 17-OHCS	→	↓	↑ ↑	↑ ↑	
Plasma ACTH	→ or ↓	↓		↑ ↑	↑↑ or ↑
Ectopic ACTH Syndrome					
Plasma cortisol	→	→	→	→	→
Urinary 17-OHCS	→	→	→	→	
Plasma ACTH	→ (remains high)	→		→	→
Primary Adrenal Tumor					
Plasma cortisol	→	→	→ or ↑	→	→
Urinary 17-OHCS	→	→	→	→	
Plasma ACTH	→ (remains low)	→		→	→

tested, but failure of ACTH or cortisol to rise after CRF has been reported in the ectopic ACTH syndrome,[10] primary adrenal tumor,[10] and bilateral micronodular adrenal hyperplasia.[9]

Very little experience has been reported in the use of CRF for delineating the cause of hypopituitarism. One patient with isolated ACTH deficiency but otherwise normal pituitary function failed to respond to CRF, while another with a known hypothalamic lesion showed a brisk ACTH response.[9] These case reports suggest that CRF may be helpful in evaluating cases of secondary adrenal insufficiency.

Doses of CRF of 200 μg or more can cause distressing side effects such as hypotension, flushing, dyspnea, and even cardiac asystole.[12, 13] These problems suggest that doses should be limited to 0.3 μg/kg or 100 μg where side effects are mild and uncommon.

There have been no reports in which CRF has been used therapeutically as a means of restoring adrenal function in patients with secondary adrenal insufficiency. Although CRF appears to have a much longer half-life than most of the other hypothalamic releasing factors when given to man,[13] its use in place of cheaper and more easily administered adrenal glucocorticoids appears improbable in the near future. In this early stage of our knowledge, extrapituitary effects of potential therapeutic value cannot be ruled out.

Growth Hormone-Releasing Factor (GRF)

Because of its potential usefulness in the treatment of dwarfism due to growth hormone deficiency, the isolation of the hypothalamic factor that stimulates growth hormone (GH) secretion by the pituitary has been eagerly awaited. Attempts over the past 20 years to purify GRF from animal hypothalami, however, have been unsuccessful, primarily because of the minute quantities present. A long awaited breakthrough came in November 1982, when investigators at the University of Virginia reported the isolation of a peptide with GH releasing activity from a human pancreatic tumor.[14] The patient, a 21-year-old woman, presented with signs and symptoms of acromegaly. Her serum growth hormone levels were markedly elevated and her serum somatomedin-C, the GH dependent peptide that is believed to mediate the growth promoting actions of GH, was nearly 10 times normal. Since her sella turcica was enlarged, a pituitary GH-secreting tumor was suspected. Pituitary tissue removed by transsphenoidal surgery, however, revealed hyperplasia of the GH-secreting cells, rather than a discrete adenoma. Furthermore, the patient's acromegaly persisted after operation, and a search was made for an ectopic source of GRF. A CT scan of the abdomen showed a 5 cm tumor in the tail of the pancreas. Within hours following its removal there was a dramatic fall in serum GH concentrations. Cell culture medium in which pieces of the tumor were incubated caused the release of GH from cultured rat pituitary cells.

Within weeks following the report of this patient with apparent ectopic GRF secretion, the amino acid structure of the active peptide that had been purified from the patient's tumor was determined.[15] This peptide, referred to as hpGRF because of its origin in the human pancreas, has 40 amino acid residues. Based on sequence homologies this GRF is closely related to the glucagon-secretin family of peptides derived from the gut. Several synthetic replicates of varying length from the N-terminus of hpGRF possess full biological activity, suggesting the biological function depends on the amino acids nearest the C-terminus of the molecule.

Concurrent with the studies outlined above, Sassolas and colleagues in Lyon, France obtained a large islet cell carcinoma from the pancreas of another patient with the clinical picture of acromegaly. Studies of this tumor done by Guillemin and his associates at the Salk Institute resulted in the isolation of the same 40 amino acid residue peptide. In addition, this tumor contained a 44 amino acid peptide with even greater *in vitro* GH-releasing activity than the 40 residue peptide,[16] and a 37 residue peptide with somewhat less *in vitro* activity.[17] Since all three peptides had identical sequences from their N-terminus, it was postulated that

hpGRF-40 and hpGRF-37 were biologically active fragments of hpGRF-44.[18]

Although not yet proven, there is increasing evidence that pancreatic GRF is structurally identical with hypothalamic GRF. The active material extracted from the two sources behaves identically on gel chromatography. Using antibodies raised against pancreatic tumor GRF, and immunohistochemical techniques, it has been possible to localize GRF in neuronal cell bodies in the hypothalamus of several species. The axons of these neurons project to the median eminence and end in contact with the portal vessels connecting the hypothalamus with the pituitary.[19]

Actions of GRF In Vivo. The first *in vivo* studies on the action of GRF were done in anesthetized rats. As little as 33 ng of GRF-44 administered intravenously caused a detectable increase in serum GH in less than 5 minutes.[20] Using an iv dose of 55 ng GRF, the serum GH rose from basal values of $\simeq$ 200 ng/ml to 9000 ng/ml. Despite their difference in *in vitro* potency, GRF-44, GRF-40 and GRF-37 were equipotent *in vivo*.

Studies in rats were quickly followed by observations on GH release following iv GRF administration (1 μg/kg) to healthy men.[21] In these experiments, serum GH concentrations were increased within 5 minutes. Beginning at preinjection levels of 2 ng/ml or less, GH levels peaked at 20.4 $\pm$ 6.5 ng/ml between 30 and 60 minutes. Serum levels of a variety of other hormones were unchanged by administration of GRF, attesting to its biological specificity.

GRF as a Diagnostic and Therapeutic Agent. Many patients who suffer from GH deficiency have primary lesions of the hypothalamic-GH regulatory centers, rather than destructive pituitary lesions. In these patients there is radiologic or pathologic evidence of lesions localized to the hypothalamus. In other patients with so-called idiopathic hypopituitarism, the most common form of GH deficiency in children, there is almost invariably a normal increase in serum TSH levels after the intravenous administration of thyrotropin-releasing hormone (TRH). This implies that at least for TSH secretion, the pituitary itself is intact. Therefore, it is not surprising that when GRF is administered to a variety of hypopituitary patients, some show an increase in serum GH.[22, 23] Although studies are not yet sufficient to draw firm conclusions, it appears that measurement of the GH response to GRF will be useful in determining whether patients with impaired GH secretion have hypothalamic or pituitary lesions. In general, however, responses in all hypopituitary patients are much less pronounced than in normal subjects.

When GRF is given to patients with acromegaly, two types of serum GH responses may be observed.[24] One group of patients shows rises in GH similar to those of normal subjects. These patients also show at least a 20% decline in GH in response to glucose. The second group has supernormal rises in GH, and only a small decline or a paradoxical increase in GH after administration of glucose. It is possible therefore that an exaggerated response to GRF is indicative of more active disease.

Thus, GRF already shows promise as a diagnostic tool. It should prove useful in localizing the functional lesions causing GH deficiency, and perhaps in distinguishing different forms of acromegaly. To date, studies are so preliminary that the eventual role of GRF as a diagnostic agent cannot be precisely defined.

The peptide also offers promise as a form of treatment for patients who have GH deficiency due to hypothalamic disease. It is theoretically possible that chronically administered GRF could normalize GH secretion in such patients, restoring growth. It is also possible that GRF could prove useful in increasing GH secretion in a variety of patients with catabolic disease states, thereby promoting nitrogen retention or wound healing.

Summary. Both CRF and GRF are invaluable probes for defining the mechanisms regulating the secretion of ACTH and GH. In addition, their use in patients with endocrine disorders promises to provide new means for precisely defining the nature of a variety of illnesses. Finally, each has therapeutic potential. The opportunity is at hand to perform the studies needed to bring CRF and GRF to their full potential in the care of patients.

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SCIENTIFIC ARTICLE

An Uncommon Cause of Hematuria: The Patient's Story

Richard A. Davidson, M.D.

A 51-year-old counseling psychologist presented to North Carolina Memorial Hospital with the chief complaints of hematuria, decrease in exercise tolerance, generalized malaise, and recent onset of mild hypertension. The hematuria was first noted six months prior to his visit; it was initially noted as being just a mild discoloration of urine; microscopic evaluation at the health clinic which employed the patient revealed mild hematuria, which waxed and waned until he sought care. His systemic symptoms began around the same time; the patient jogged daily, and noted a definite change in his exercise capacity. One month prior to his visit he was found to be mildly hypertensive, with blood pressure measurements in the range of 140/95. Routine lab evaluation revealed a normal hematocrit and white blood cell count. The patient was seen by a urologist, who scheduled the patient for an IVP and cystoscopy. Prior to those procedures, he sought a second medical opinion. The patient lived in Chapel Hill, but questioning revealed that he and his wife had visited his son, who was in the Peace Corps in Swaziland, Africa, approximately 9 months prior to the onset of his symptoms. While in Africa, they had on one occasion gone swimming in a fresh water lake near their son's home. Twenty-four hour urine collections from the patient and his wife were evaluated by Dr. Norman Weatherly of the University of North Carolina School of Public Health and revealed the presence of eggs of *Schistosoma haematobium*. Both were treated with praziquantel in a dosage of 60 mg/kg/day, in three divided doses. Within 3 weeks, the patient noted a dramatic improvement in his systemic symptoms. Follow-up urine specimens were negative for parasites 2 months after treatment.

Discussion

In previous articles I have discussed case series of common human parasites seen at North Carolina Memorial Hospital. While these parasites represent the vast majority of cases diagnosed in our laboratory, more exotic parasites are occasionally seen; there have been four cases of schistosomiasis diagnosed at NCMH in the past four years.

There are four schistosomes that cause systemic infection in humans: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma mekongi,* and *Schistosoma haematobium*. They are found in various parts of the world, including the Middle East, Africa, the Philippines, the Caribbean, Southeast Asia, Japan, and China. These parasites are blood flukes, and have an extremely complicated life cycle which includes an asexual stage in a specific aquatic snail as an intermediate host, and a sexual stage in humans, the definitive host. All infections are transmitted through exposure to infected water, and the sexual forms that penetrate skin and cause the infection mature in the blood stream, mate in the liver, and live in venous plexuses; *S. mansoni, S. mekongi,* and *S. japonicum* live in the venous plexuses of the gut, and involve the portal circulation and the liver, causing hepatomegaly, portal hypertension and esophageal varices. *S. haematobium* lives in the venous plexuses of the bladder, causing hematuria, obstructive uropathy, and an increased risk of carcinoma of the bladder. Pathologically, the disease is an immunologic disorder in which the host response to the schistosome eggs causes fibrosis and granuloma formation.[1] The infection is chronic, and Pearson and Guerrant[2] estimate that 200 million people are infected worldwide, with 400,000 infected persons in the continental United States.

The diagnosis is made by finding the characteristic large eggs, with lateral or terminal spines depending on the species, in stool or urine. Patients may initially present with non-specific symptoms including fever and malaise; a travel history is essential in order to consider the diagnosis. Three stools will usually reveal the presence of gastrointestinal schistosomiasis; large amounts of urine should be concentrated to evaluate patients for *S. haematobium* infection.

Treatment of schistosomiasis has been extremely difficult in the past; the drugs which were most frequently used, metrifonate for *S. haematobium,* oxamniquine for *S. mansoni,* and antimony compounds for *S. japonicum,* are all toxic and have variable cure rates. A new drug, praziquantel (Biltricide; Miles Pharmaceuticals), is effective against all forms of *Schistosoma* species,[2, 3] and is also effective against other trematodes and cestodes, including *Taenia* species, *Diphyllobothrium latum,* cerebral and visceral cysticercosis,[4] and probably lung and liver flukes. The drug is usually given in three divided doses in one day for the treatment of schistosomiasis, but single treatments with as low as 5 mg/kg are effective against many cestodes. The drug may cause gastrointestinal upset, malaise or headache, but has not been found to have long-term toxicity. It is a welcome addition to the armamentarium of anthelminthic drugs.

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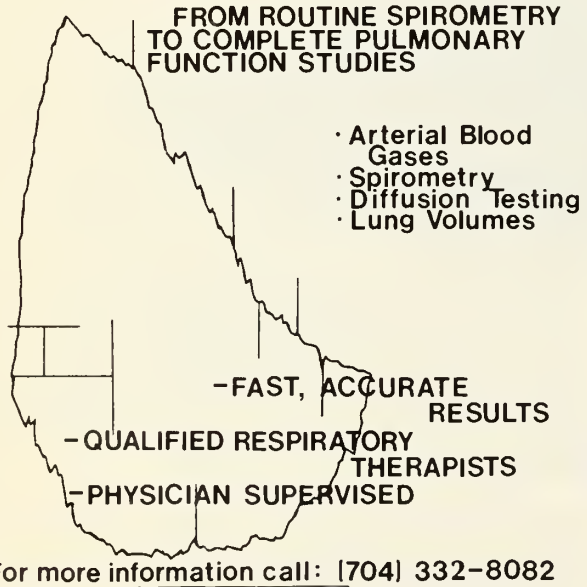
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BRIEF SUMMARY

PROCARDIA® (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: **I. Vasospastic Angina**: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: **Excessive Hypotension**: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: **General Hypotension**: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients. Transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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Quotes from an unsolicited letter received by Pfizer from an angina patient. While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.

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J-4044 January 1984

SCIENTIFIC ARTICLE

Arm Drift — A Frequent Occurrence in Normal Subjects

E. Wayne Massey, M.D., Barbara Scherokman, M.D., and Janice M. Massey, M.D.

ASSESSMENT of arm "drift" (defined as any degree of arm "sag" or rotation (pronation) that could be observed during the set time period) is a part of the usual neurological examination. Distinct asymmetry of arm drift with arms extended at rest is usually noted in recording the neurologic examination, particularly when the history or examination is compatible with impairment of the lesser moved extremity. However, characteristics of arm drift among the normal population has not previously been studied formally.[1]

Methods

An assessment of arm drift with the arm raised horizontally in front of the examinee was designed to duplicate conditions of the standard neurological examination. A total of 153 volunteers, 65 female and 88 male, ages 19-55, were asked to participate. The subjects with any history of prior neurological disorder were excluded. Sixty-five individuals underwent complete neurological examination by at least one examiner with normal results. Subjects with abnormal neurological examinations were excluded from the study. After observation and recording, each subject was then asked to complete a questionnaire which inquired as to his or her handedness, previous orthopaedic or head injury, surgery to either upper extremity, or history of meningitis or encephalitis. History of seizures, operation or illness excluded a subject from tabulation. No hospitalized or neurology clinic patients were included. No specific purpose of the study was disclosed to subjects.

The drift of each subject was assessed by one of three observers as would be done in the course of a neurological examination. Each fully clothed subject was asked to extend the arms horizontally in front of him with palms up, eyes closed and feet together. The elbows were fully extended, as were the wrists, and the hands were open with the palms up. Slow pronation of the wrist accompanied by slight flexion of the elbow and downward and lateral drift of the hand was defined as "arm drift" when observed.

TABLE 1

	Handedness	
	Right	Left
Right drift	91 (64%)	0
Left drift	8 (6%)	9 (75%)
No drift	42 (30%)	3 (25%)
Total	141	12

From the Division of Neurology, Duke University Medical Center, Durham (Drs. Massey) and Department of Neurology, Uniformed Services University of Health Sciences, Bethesda, MD (Dr. Scherokman).

They were observed for a period of 20-30 seconds on each occasion. The examination recorded only movements considered obviously asymmetric, although no attempt at quantitation was made. Examiners were unaware of the subject's hand preference.

Results

Twelve were left-handed. One hundred and forty-one were right-handed individuals. The assessment of each examiner was tabulated (table).

Among right handed subjects, 64% had a predominant drift on the right and 30% had no evident drift. The sample was not of sufficient size in left-handed individuals but none had more drift on the right in this small sample. Differences in right versus left were not influenced by age or sex of the subjects.

Comment

An attempt was made to duplicate procedures of the neurological examination. Therefore, although questioning the subject about handedness does not unequivocally establish cerebral dominance, the determination delineates this function as clearly as in routine clinical assessment. Routine neurological examination in 65 individuals supported their history of handedness.

The methods utilized obviously do not completely exclude neurological deficit in all participants. Sixty-five patients had a normal neurological examination. The sample was taken from a large, non-patient group, predominantly young adults who had no history of orthopaedic or major neurological disease. Grossly abnormal paresis, abnormal gait mechanisms, or hemisensory involvement seen in neurological disease were not encountered in any of the 95 subjects not examined.

Wartenberg[1] suggested that in many normal individuals some asymmetry of drift exists. Similarly, arm swing asymmetry may be present in normal individuals[2] and other asymmetries have been noted in neurological testing.[3]

It is apparent from our evaluation that an asymmetrical "drift" movement during neurological examination is not of itself an abnormal sign. To the contrary, bilateral equal movements are present in only a third of the group. A majority of healthy young adults who consider themselves right handed actually drifted their preferred right arm more than their left.

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SCIENTIFIC ARTICLE

The Identity and *in vitro* Antibiotic Sensitivity of Aerobic Gram-Negative Rods in a Community Hospital

Charles Ellenbogen, M.D. and Susan C. Hester, B.S., M.T.

THE best antimicrobial agent with which to treat an infection due to aerobic gram-negative rods (GNR) is one to which the causative microorganism is sensitive.[1] However, serious systemic infections due to GNR may require institution of antimicrobial therapy before the results of bacterial culture and sensitivity are completed by the microbiology laboratory and therefore before the prescribing physician can know the identity and antimicrobial sensitivity of the causative GNR. The physician's initial antimicrobial prescription in this setting can be made more rationally if the physician can accurately surmise the microorganism(s) that is most likely to be the cause of serious infection at a given anatomic site and the antimicrobial agent that is most likely to be effective against it.[2, 3] Published reports of such data often originate from tertiary care medical centers.[4-8] The identity and antibiotic sensitivity of microorganisms, especially GNR, which are most likely to cause infections in patients hospitalized in a tertiary care medical center, may not necessarily be the same as those causing infection in a community hospital.[9] The purpose of this report is to present a limited description of GNR causing infections and their antimicrobial sensitivities in a community hospital in North Carolina.

Methods and Materials

Gram negative rods (GNR) isolated from clinical specimens were speciated using API (20E) strips. Isolates were stored on nutrient agar slants at 4 degrees C and tested for antimicrobial sensitivity in batches of 40.

Antimicrobial testing was performed according to the methods and standards of the National Committee for Clinical Laboratory Standards (NCCLS M2-825, Volume 2, Number 2, March 1982). Discs containing antimicrobial agents were purchased from Becton-Dickenson Company and stored in a dessicator at 4°C. Batches of organisms were tested with control organisms ATCC strain 29522 *E. coli* and ATCC strain 27853 *Pseudomonas aeruginosa*. For testing, organisms stored on nutrient agar slants were grown up on MacConkey agar. Three to five colonies were then picked using an inoculating loop, transferred to tryptic soy broth and incubated at 35°C for 24 hours until turbidity was equivalent to 0.5 barium sulfate. This suspension was used to inoculate a Mueller-Hinton agar plate as described by NCCLS. Isolates were characterized as resistant, intermediate or sensitive using NCCLS standards.

Antimicrobial agents tested in our laboratory on routine clinical isolates of GNR include aminoglycosides (Gentamicin and Tobramycin), previously available penicillins (Ampicillin and Carbenicillin), and cephalosporins (Cephalothin and Cefamandole). Other agents are also routinely tested but are not reported because of the rarity of either their indication or their use as primary agents for the therapy of systemic infection caused by GNR: Kanamycin, Tetracycline, Chloramphenicol, Colistin, and Trimethoprim/Sulfamethoxazole. Separately tested were Amikacin, newer penicillins (Mezlocillin, Azlocillin and Piperacillin) and cephalosporins (Cefoxitin, Cefotaxime, Cefoperazone, and Moxalactam) and then only on isolates found to be multiply resistant upon routine testing or upon the request of the physician.

Testing for this study was rigorously controlled through both batch testing as described and simultaneous testing of all agents. Limitations in the time and manpower available to perform testing in this way limited the total number of isolates that could be tested to 200.

Results

Table 1 describes the GNR isolated according to the site from which the culture was obtained. Not described in table 1 are the two GNR isolated in blood cultures — *Klebsiella pneumoniae* and *Salmonella indiana*.

E. coli is the most common isolate, especially from urine and from wound and skin infections. *Pseudomonas aeruginosa* was the second most common and *Pseudomonas fluorescens* the fifth most common isolate jointly accounting for 16% of the total. These pseudomonads were especially important in nosocomial infections of the skin (including surgical wounds) and of the respiratory tract. *Proteus mirabilis* and *Klebsiella pneumoniae* were almost exclusively urinary pathogens and each accounted for less than 10% of the total. Other organisms were even less common with the exception of *Salmonella typhimurium* which was exclusively a stool isolate. The blood isolate of *Salmonella indiana* was not isolated from the patient's stool. The other less commonly isolated organisms were either predominantly urinary pathogens or demonstrated no specific site-pathogen association.

Table 2 contains the percentage of the five most fre-

From the Fayetteville Area Health Education Center and Cape Fear Valley Medical Center, Fayetteville 28306.

Table 1
Facultative (Aerobic) Gram Negative Rods Isolated on Culture by the Site of Origin of the Culture

	Number of Isolates				
	Urine	Wound/ Skin	Sputum/ Respiratory	Stool	All Sites
Sample n:	146	21	16	11	200
E. coli	67	9	3	2	82
Pseudomonas aeruginosa	11	4	4	1	20
Proteus mirabilis	16	1	1	0	19
Klebsiella pneumoniae	13	0	2	1	17
Pseudomonas fluorescens	9	1	1	0	12
Enterobacter aerogenes	6	0	0	0	7
Citrobacter freundii	3	2	0	0	5
Salmonella typhimurium	0	0	0	5	5
Enterobacter cloacae	3	1	1	0	5
Acinetobacter calcoaceticus	4	0	1	0	5
Serratia marcescens	4	1	0	0	5
Klebsiella oxytoca	2	0	1	0	3
Morganella morganii	2	1	0	0	3
Pseudomonas sp.	2	1	0	0	3
Serratia liquefaciens	2	0	0	0	2
Shigella sonnei	0	0	0	1	1
Salmonella indiana	0	0	0	0	1
Providencia stuartii	1	0	0	0	1
Proteus rettgeri	1	0	0	0	1
Klebsiella ozaenae	0	0	1	0	1
Proteus vulgaris	0	0	0	1	1
Pseudomonas cepacia	0	0	1	0	1

quently isolated GNR that were susceptible to each drug. Some of the percentages have a superscript. The disc sensitivity method describes bacteria as either sensitive, resistant or intermediate. The intermediate level of sensitivity (to which the superscripts refer) is of marginal clinical value and is therefore reported separately.[10]

Aminoglycosides are the most uniformly effective antibiotics; however, Gentamicin and Tobramycin resistance is seen among pseudomonas isolates. Against these resistant isolates Amikacin, Cefoperazone and Piperacillin are the most efficacious (table 3). Against *E. coli, Klebsiella pneumoniae* and *Proteus mirabilis* Cefamandole, Cefoxitin and to a lesser degree even Cephalothin are as effective as either Cefoperazone and Moxalactam or Piperacillin and Mezlocillin.

Many additional GNR were isolated in small numbers (table 1). When their antibiotic sensitivities (data not shown) are combined with those in table 2 a site-sensitivity association is derived (table 4). These data combined the frequency of isolation of the bacteria at each site (table 1) and their sensitivity (table 3) including the less common isolates.

Table 2
Antibiotic Disc Sensitivity to Most Common Facultative (Aerobic) Gram Negative Rods

	Percent Susceptible*				
	E. coli	Klebsiella pneumonia	Proteus mirabilis	Pseudomonas aeruginosa	Pseudomonas fluorescens
Sample n:	82	17	19	20	12
Amikacin	96%	100%	100%	100%	83%
Tobramycin	100%	100%	100%	75%	67%
Gentamicin	100%	94%	100%	70%	67%
Cefoperazone	94%[1]	88%	100%	90%	58%
Moxalactam	100%	88%	100%	30%[1]	33%[2]
Mezlocillin	84%	88%	95%	75%[2]	50%[3]
Piperacillin	77%[2]	82%[2]	89%[2]	95%	75%
Cefotaxime	98%	82%[3]	100%	10%[2,3]	25%[3]
Cefamandole	96%	94%	95%	0%	0%
Azlocillin	72%[2]	35%[2,3]	95%	95%	75%
Cefoxitin	96%	88%[2]	100%	0%	17%
Carbenicillin	72%	0%	100%	65%[2]	58%[2]
Keflin	73%[1,3]	94%	95%	0%	0%
Ampicillin	70%	0%	89%[2]	0%	0%

* Fewer than 5% of isolates possess intermediate susceptibility except as follows:
[1] 5 to 9% of isolates possess intermediate susceptibility.
[2] 10% to 12% of isolates possess intermediate susceptibility.
[3] 14% to 29% of isolates possess intermediate susceptibility.

Table 3
Susceptibility of Gentamicin-Tobramycin-Resistant Facultative (Aerobic) Gram Negative Rods to the Newer Cephalosporins and Penicillins

	Number of 18 isolates resistant to either Gentamicin or Tobramycin or both*		
	Sensitive	Resistant	Intermediate
Amikacin	14	3	1
Cefoperazone	14	2	2
Moxalactam	5	3	10
Mezlocillin	10	6	2
Piperacillin	13	5	0
Cefotaxime	4	7	7
Azlocillin	11	6	1
Carbenicillin	6	10	2

* 6 Pseudomonas aeruginosa; 4 Pseudomonas fluorescens; 3 Pseudomonas sp.; 1 each Pseudomonas cepacia; Proteus rettgeri; Klebsiella pneumoniae; Serratia liquofaciens; Providencia stuartii.

Table 5 describes the total cost per day to the patient receiving intravenous antibiotic therapy at the dosage and frequency recommended for the treatment of serious systemic infections.

Table 5
Cost of One Day of Intravenous Antibiotic Therapy

Drug	Dose	Interval Between Doses (hours)	Cost*
Amikacin	500 mg.	12	$68.76
Gentamicin	80 mg.	8	$69.54
Tobramycin	80 mg.	8	$73.38
Cefazolin	1 gram	8	$76.26
Moxalactam	2 grams	8	$118.23
Cefoperazone	2 grams	8	$124.68
Cefotaxime	2 grams	6†	$144.72
Ampicillin	1 gram	4†	$130.14
Cefamandole	1 gram	4†	$149.70
Cefoxitin	1 gram	4†	$163.26
Cephalothin	2 grams	4†	$132.96
Piperacillin	3 grams	4†	$167.88
Carbenicillin	3 grams	4†	$158.34
Ticarcillin	3 grams	4†	$165.06
Mezlocillin	4 grams	4†	$200.40

* Includes direct cost of drug plus pharmacy admixture charge.
† Dosage for 70 kg adult with normal renal function and a clinical infection of moderate or intermediate severity or worse using Table 2 from *Annals of Internal Medicine* 1983;98:530-535.

Discussion

When a physician is caring for a patient whose clinical findings suggest a serious systemic infection due to GNR which requires immediate antibiotic therapy, one of the first steps is to collect and process those specimens of tissue or tissue fluid, such as blood, urine or cerebrospinal fluid, from which causative microorganisms can be cultured and sensitivity tests performed.[1, 2] However, since it will be 24 or 48 hours before the initial results of these tests become available, the immediate selection of the initial antimicrobial agent must be made on other data. Such data as is reported here will permit the prescribing physician to surmise the likely pathogens and to select the antibiotic(s) which is most likely to be effective. Moreover, combining these data with information about the cost of the alternative antimicrobial agents will permit the most cost effective initial antibiotic choice. Cost can be lowered by intramuscular as opposed to intravenous administration when appropriate as well as by use of a lower dose or less frequent dosing if clinical factors warrant.

There are many other factors that bear upon the selection of an antibiotic.[3, 8] First, the physician must be aware that GNR are not the only possible pathogens for many infections and that antimicrobial agents effective against possible gram-positive pathogens and anaerobic gram-negative

Table 4
Antibiotic Disc Susceptibility of Facultative (Aerobic) Gram Negative Rods by Site of Origin of Culture

	Percent Susceptible				
	Urine	Wound/ Skin	Sputum/ Respiratory	Stool	All Sites
Sample n:	146	21	16	11	200
Amikacin	96%	95%	94%	100%	96%
Tobramycin	92%	86%	88%	100%	92%
Gentamicin	92%	86%	81%	100%	92%
Cefoperazone	96%	81%	88%	82%	85%
Moxalactam	85%	67%	56%	91%	80%
Mezlocillin	79%	81%	88%	91%	80%
Piperacillin	79%	86%	75%	82%	79%
Cefotaxime	79%	62%	56%	73%	75%
Cefamandole	74%	62%	50%	91%	72%
Azlocillin	70%	86%	63%	73%	71%
Cefoxitin	69%	43%	56%	91%	67%
Carbenicillin	63%	71%	56%	82%	64%
Keflin	56%	38%	31%	73%	54%
Ampicillin	42%	38%	6%	73%	41%

Fewer than 5% of isolates possess intermediate susceptibility except as follows:
[1] 5% to 9% of isolates possess intermediate susceptibility.
[2] 10% to 12% of isolates possess intermediate susceptibility.
[3] 14% to 29% of isolates possess intermediate susceptibility.
[4] 30% to 40% of isolates possess intermediate susceptibility.
[5] 67% of isolates possess intermediate susceptibility.

pathogens must be added when clinically appropriate.[2] Some of the newer agents may be effective against both GNR and anaerobic gram-negative bacilli permitting the use of one drug instead of two (i.e., Cefoxitin or Cefotaxime instead of Clindamycin plus Gentamicin for peritonitis).[11, 12] Second, the exact site of an infection and whether it is hospital or community acquired could be important.

For example, in our hospital a gram-negative pneumonia that is hospital acquired would likely have *Pseudomonas aeruginosa* or *Pseudomonas fluorescens* as the pathogen. This knowledge might prompt the prescriber selecting from among the newer agents to pick Piperacillin over Mezlocillin or Cefoperazone despite the apparent superiority of Cefoperazone or Mezlocillin overall against respiratory pathogens (table 4) because Piperacillin is the better anti-pseudomonas agent (table 2). However, Piperacillin and other anti-pseudomonal penicillins and cephalosporins should be prescribed with an aminoglycoside because of the danger of the development of resistance and subsequent clinical failure when used alone.[12-14]

Many host factors also bear upon antibiotic selection. Patients who have compromised immunologic function such as those who are neutropenic, or who have diseases such as sickle cell anemia or diabetes, or who have burns may require a different dosage, route or drug. Abnormalities of the function of the liver and of the kidneys bear upon the drug, dosage and route that ought to be selected.

Despite the limitations of the small number of observations reported here certain cautious conclusions seem permissible. Tobramycin and Gentamicin resistance was observed in 9% of isolates, especially pseudomonas, a rate higher than that found in another community hospital and similar to that found in some tertiary care medical centers.[4, 9] Yet these aminoglycosides remain the most effective agents against non-pseudomonal isolates. Amikacin, Piperacillin and Azlocillin are the most effective anti-pseudomonal agents. The prescriber who wishes to avoid the use of an aminoglycoside would find that the most effective antibiotics are Cefamandole or one of the third generation cephalosporins for non-pseudomonas isolates.[5]

The cost of antibiotics can be substantial (table 5). The aminoglycosides appear to be the least costly agents in our hospital. However, the cost of one ($76) or two ($152) pairs of pre-dose and post-dose aminoglycoside serum level determinations can increase the cost of 10 days of Gentamicin therapy (assuming no change in dosage or dosing frequency) from $659 to $811.

Cefamandole is less costly than either Cefotaxime or Moxalactam and may be, therefore, the beta-lactam of first choice for non-pseudomonas GNR infection. Piperacillin is the least costly anti-pseudomonal penicillin and considering its substantial overall effectiveness may be the most cost-effective beta-lactam to prescribe, keeping in mind the danger of using it alone mentioned above.[15]

In conclusion, knowing the identity and antimicrobial sensitivity of GNR by site of infection in patients at your hospital as compared with other hospitals may increase the accuracy with which you select the initial antimicrobial agent for treatment of a serious systemic infection.[2, 16]

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Cryptococcal Arthritis of the Acromio-Clavicular Joint

Renee Adams and Malcolm McDonald

Cryptococcus neoformans is distributed worldwide; as a yeast it has the potential to cause life-threatening systemic disease in man. The primary clinical form of cryptococcosis usually affects the pulmonary parenchyma, presumably due to inhalation of organisms.[1] When hematogenous spread of the infection to extrapulmonary sites occurs, the most common metastatic foci are the central nervous system, kidneys, reticuloendothelial system, skin, and bone.[2] Joint involvement is rare. We could find only 11 cases of cryptococcal arthritis described in the medical literature.[3-11]

Case Report

A 57-year-old black man was seen in March 1983 with a two-month history of increasing pain over the point of his left shoulder, associated with local swelling and tenderness. A radiograph done elsewhere ten days earlier had revealed a lytic lesion of the distal left clavicle, and fluid aspirated from the left acromio-clavicular joint showed a white blood cell count (WBC) of 217,000/mm^3, with 90% neutrophils. No organisms were found on gram stain and culture on routine media.

The patient's past medical history was significant for pulmonary sarcoidosis diagnosed in 1946 by lymph node biopsy and originally treated with radiation. He required no further therapy until 1974, when worsening dyspnea necessitated treatment with prednisone 40 mg/day. From that time, the patient was maintained on corticosteroids in varying doses. During the 6 months prior to his March 1983 admission, he had received 10 to 15 mg of prednisone every other day, and his symptoms had remained stable.

The patient was employed as a nursing aide. He had no history of exposure to pigeons and denied recent increase in cough, sputum production, or headaches.

Upon admission the patient was afebrile, but tachypneic at rest. Auscultation of the chest revealed bibasilar rales and an expiratory wheeze. The left acromio-clavicular joint was swollen and tender, but without warmth or erythema. There was only slight limitation of shoulder movement. Neurologic examination was unremarkable.

A roentgenogram confirmed erosion of the left clavicle, with total obliteration of the acromio-clavicular joint, suggesting erosive arthritis. A radioisotope bone scan showed increased uptake at the left acromion and the distal clavicle.

Laboratory data on admission included a hematocrit reading of 47.7%, peripheral white blood cell count of 6,100/mm^3, with no left shift, and a Westergren erythrocyte sedimentation rate of 3 mm/hr.

On April 8, 1983 the distal clavicle was resected and the fibrinous contents of the acromio-clavicular joint were removed. Histologic examination showed acute and chronic inflammation with histiocytes and giant cells. Fungal stains demonstrated budding yeasts with alcian blue-positive capsules. *Cryptococcus neoformans* was cultured from the surgical specimen. The organism was not recovered from cultures of blood or cerebrospinal fluid (CSF). Cryptococcal antigen could not be demonstrated by latex agglutination in samples of serum or CSF.

The patient was treated with a combination of amphotericin B and 5-fluorocytosine (5-FC). A total of 900 mg of amphotericin B was given over six weeks, together with 5-FC at a dose of one gram every six hours. He reported progressive decrease in left shoulder pain over the course of his therapy and was discharged pain-free in April 1983 to be followed in the Medical Outpatient Clinic.

Discussion

Cryptococcal arthritis was first described by Von Busse in 1894 when he made the observation in a case report that a "sarcomatous" lesion of the tibia had presumably eroded into the knee joint.[4] Since that time very few cases of cryptococcal joint infection have been described; to our knowledge there are only eleven in the literature. The incidence of joint involvement is less than one would expect, since osteomyelitis due to hematogenous spread of cryptococcus occurs in approximately 10% of cases of systemic cryptococcosis.[12]

This case demonstrates several key points about cryptococcal arthritis. As in other cases reviewed, the disease was subacute in its presentation, with signs and symptoms of synovitis, but without further evidence of metastatic infection.[13] Pulmonary symptomatology and an abnormal chest roentgenogram have been noted in half of the cases, although it is not always possible to distinguish between underlying pulmonary disease and pulmonary cryptococcosis. This is particularly true when the patient, as in this instance, has sarcoidosis. The association between cryptococcal osteomyelitis and sarcoidosis has been well described.[14] Corticosteroid treatment of sarcoidosis is an additional aggravating factor. The conclusion drawn from previous reports that cryptococcal arthritis is secondary to adjacent bone infection agrees with the finding, in this case, of a lytic lesion in the distal clavicle in close proximity to the acromio-clavicular joint. This case demonstrates

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an excellent response to a combination of amphotericin B and 5-FC, taking advantage of the reported synergistic effect of the two drugs,[15] while reducing the amount of potential toxicity due to amphotericin B.

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The Durham Connection to Germany

Walter Kempner M.D.

Thoughts Upon Looking at the 1983 Commemorative Issue of the Postal Service of West Germany in Honor of The Hundredth Birthday of Otto Warburg, the Father of Cellular Physiology

"HERE in the Medical School of Heidelberg everybody wants to be a Professor and wants to teach and wants to talk. There was never anybody here who wanted to work. When something finally has to be done, they shout: 'Mr. Ziegler, Mr. Ziegler!' Doctor, I get sick to my stomach when I hear my name."

Mr. Ziegler was the janitor who cleaned my glassware when I was an intern in Heidelberg where I did blood sugar determinations on dogs I had made diabetic by the injection of phlorizine. Mr. Ziegler had a fine upright character and I learned a lot from his pearls of wisdom, even when he was not completely sober and wore his hat on the back of his head while washing the pipettes and flasks.

I said, "Really, really, Mr. Ziegler, in all the time you were here wasn't there ever anyone who did some work?" After a lot of deliberation he said, "Yes, several years ago there was one, but he left pretty soon and never became a Professor; and one never heard anything about him anymore."

Sitting in the library a few days later, I looked to see if he had ever published a scientific paper and came across something about sea urchin eggs, nucleated red blood cells, and metabolic reactions of cancer cells. All of a sudden I found myself writing a letter to this unknown man whose address was in Dahlem, a suburb of Berlin, asking him whether I could work in his laboratory. He answered me politely that unfortunately he had only a very small laboratory where there was no space, but he would be glad to talk with me if I should come sometime to Berlin.

My ward consultant said that this was the most complete nonsense he had ever heard especially in my case since the big boss, Dr. von Krehl who had written the famous first book about pathological physiology (which incidentally was translated into English with an introduction by Osler), wanted to put me on the Staff as soon as I finished my internship. But I protested and said that I first wanted to learn something. My superior said, "It is much more important for your career to have been on the boss's Staff a few years than to learn everything." Anyway, I took the train to Berlin and Warburg talked with me in his small office. He was 43 years old, I was 24. He asked me, "Do you know any mathematics?" I said no. "Any physics?" I said no. "Any chemistry?" I said no. He said, "What actually do you know?" I said, "I graduated from the Medical School in Heidelberg and completed my internship there, and I published a paper about diabetes and did more than 650 blood sugar determinations on a dozen dogs and a few rabbits. (The methods were not so simple then and I had to do all the determinations myself without the help of technicians.) So I really don't know anything." Warburg said, "At least you are honest. But you will see for yourself what I already wrote you that this is a very small laboratory and there is no space for anybody else. However, you can stay here for a couple of weeks and learn our methods."

There were three young men without any previous training working there and three who had doctoral degrees. One was Dr. Wind who died of tuberculosis shortly afterwards; the second was Dr. Hans Gaffron, later well known for his work on photosynthesis, who was for many years Professor of Biochemistry at the University of Chicago; the third was Dr. Hans Adolf Krebs who became famous for his citric acid cycle and got the Nobel Prize a few years later. (Two other Nobel laureates had also started in Warburg's laboratory: Otto Meyerhof and Hugo Theorell).

After the two weeks were over, Warburg asked me, "Did you learn our methods?" I said no. He asked "Why not?" I said I would need much more time to learn them. He asked, "How much time would you need?" I said, "Maybe one or two years." "All right," he said, "then stay here." And I stayed there 1927 and 1928 in his small laboratory in the upper floor of the Kaiser Wilhelm Institute of Biology in Berlin-Dahlem and again in 1933 after an interval of five years in which I had been an Assistant Physician in the Medical School of Berlin.

In 1931 Warburg had got the Nobel Prize for his work on the respiration ferment and had been given a beautiful new institute of his own — the Kaiser Wilhelm Institute for Cellular Physiology in Dahlem.

Up until then he had published two books: *Metabolism of Tumors* (1926) and *Catalytic Effects of Living Substance* (1928). These books do not contain any opinions or discussions but are merely collections of the original papers he had written about the methods and results of his new experiments. One of his favorite remarks when he read the "literature" was, "There are two kinds of chemistry — experimental chemistry and paper chemistry."

The titles of his later books (1948-1962) (also collections of original papers) are: *Heavy Metals as Active Groups of Enzymes, Hydrogen-Transferring Enzymes,* and *Further Developments in Methods of Cellular Physiology.*

In 1933, after Hitler came to power in Germany, a gentleman from the Rockefeller Foundation visited Warburg in his laboratory in order to persuade him to come to the United States. Warburg looked around and said, "Here

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I know where each piece of apparatus is; here I can put my hand on everything I need," whereupon the visitor replied, "We will photograph the whole laboratory just as it stands down to the last detail. We will present you with an exact duplicate of your Institute." But Warburg couldn't make up his mind and remained in Germany throughout the rather unpleasant years before and during World War II.

Great scientists can be very average and boring people. Warburg was interesting. In 1927, my first year with him, I discussed in the evening with Dr. Krebs the results of an experiment I had just made that day. "There must be a mistake," Krebs said. I questioned why and he answered, "This is against all the laws of cellular physiology." The next morning when Warburg had come in, he asked me for the results of my experiment. I showed it to him and he said in English, "That's very exciting." I argued with my newly acquired wisdom, "But it can't be true; this is against all the laws of cellular physiology." Warburg pondered a moment and then said, "Of course you have to repeat it six or seven times, but if it always comes out the same the laws of cellular physiology have to be changed."

In 1968, the year he became 85 years old, he sent me a letter for my 65th birthday and wrote, "In many respects I found that age is better than youth. The fight for existence is over and, if one possesses luck and reason, one can still live for many years. A bank account is desirable, a house of one's own is desirable, the possibility to do scientific work is desirable. I assume that you have all of this in ample measure. And so I dare to congratulate you."

"Luck and reason." But I think I would never have been lucky in any endeavor in medicine without those years 1927, 1928, and 1933 with Otto Warburg.

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Double, Triple, Toil and Trouble — Darvocet Intoxication

Ronald B. Mack, M.D.

WITH apologies to the Bard of Avon, this month's lesson will discuss *Darvocet* overdose. For those who do not already know, *Darvocet* is composed of *Darvon* (propoxyphene) and *acetaminophen*. In an overdose situation with this medication, we must deal with propoxyphene intoxication and acetaminophen intoxication and the problems created by their combination — hence the triple "toil and trouble."

Darvon — propoxyphene — is a centrally acting *synthetic narcotic* analgesic agent that is structurally similar to methadone except that it has relatively minor properties as a narcotic. There are currently two forms of this medication: (1) propoxyphene HCl, and (2) propoxyphene napsylate (Darvon-N). 100 mg of the napsylate has the equianalgesic effect of 65 mg of the HCl form. Over the years many questions have been raised concerning propoxyphene's efficacy as an analgesic. There is a fair amount of literature that suggests that Darvon is a weaker analgesic than codeine or even salicylates. It is stated that this drug is ⅓-½ as potent as codeine in relieving pain, that in doses less than 65 mg it is no more or less effective than a reasonable dose of aspirin. 200 mg of propoxyphene-N is felt to be better than placebo in ameliorating pain, however. In fact, Darvon is rather typically prescribed in combination with another analgesic such as aspirin or acetaminophen.

In spite of its less than ideal pain relieving attributes, Darvon products are very popular prescription drugs. However, propoxyphene is also a very common factor in drug associated deaths, the majority of which are suicides, and is probably only second to barbiturates in terms of its association with suicides and accidental death. It is also true that a very large proportion of propoxyphene related deaths appear to have occurred when this drug was ingested with ethanol and/or other CNS depressants. In addition to its acute overdose problems, Darvon has addictive potential, and physical dependence and narcotic withdrawal features occur with relatively chronic use, e.g., 600-800 mg daily over an 8 week period. A narcotic withdrawal syndrome can occur in neonates whose mothers are "users" of this drug. Dependence on this drug is not common, however, as the dose needed to produce physical dependence is associated with intolerable side effects. So far the drug is only available in oral form and is extremely damaging to veins if injected IV by the "serious" addict.

The adverse effects of propoxyphene include vertigo, drowsiness, nausea and vomiting; less commonly, delusions, visual hallucinations, dysphonia, disorientation, abdominal pain and constipation can occur. (Nothing worse than being disoriented and constipated at the same time.) In *serious overdose,* however, propoxyphene produces the classic narcotic triad: (1) *coma,* (2) *respiratory depression* and (3) *miosis.* There are often some differences, however, between this classic triad and Darvon O.D. For example, *mydriasis* instead of miosis is not an uncommon event and *grand mal* or *focal seizures* are not unusual at all. The drug is rapidly absorbed and bound to tissues. Signs of overdose can occur as early as 30 minutes after ingestion and last easily 8-12 hours. As in other narcotic O.D.'s, non-cardiogenic pulmonary edema is a frequent visitor. A dose of 1-2 grams taken acutely by an adult can result in respiratory depression and seizures. Ingestions as little as 10.7 mg/kg have caused toxicity; at 35 mg/kg cardiorespiratory arrest has been reported.

The treatment of propoxyphene overdose involves: (1) gastric emptying, (2) activated charcoal, and (3) naloxone. The use of gastric emptying in propoxyphene overdose can be very tricky; because of the propensity for coma, seizures and respiratory depression soon after an overdose, very "cautious" gastric lavage would seem to be the wiser course. Activated charcoal works quite nicely here to bind the ingested propoxyphene remaining after gastric emptying. There are some good animal studies that suggest that repeated doses of activated charcoal could be quite beneficial in the treatment of this problem, i.e., repeated doses of 100-200 grams of activated charcoal, administered via N-G tube, in the first few hours post ingestion. In addition to providing respiratory support, the "big gun" used in the treatment of propoxyphene overdose is *naloxone* (Narcan), a very effective, safe, narcotic antagonist. The main objective of naloxone therapy is to produce a distribution of this antagonist sufficient enough to displace the intoxicating narcotic from its attachment to the narcotic receptor sites. Because naloxone is relatively safer, even in mega-doses, the recent recommendations concerning its use suggest increasing the dose. Therefore, for adults or children, administer initially 0.8 mg IV followed by 2.0 mg as needed. For those narcotics with longer half-lives (T½), such as Darvon, one could consider using continuous IV infusion of naloxone, e.g., 4 mg/liter of naloxone at a rate of 400 μg/hr (0.4 mg/hr) with less total fluids given (as indicated) to smaller children. Naloxone has a short T½ of 30-60 minutes vs a T½ of 12 hours for Darvon. Dialysis is ineffective because of the large volume of distribution of

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propoxyphene. It is well to remember that one of the differences between propoxyphene and other opiate derivatives is the fact that propoxyphene can require much more naloxone to reverse the adverse effects. The seizures should be treated with naloxone initially. Serum and urine levels do not relate well to the amount of drug ingested or the degree of poisoning. Pharmaceutically speaking, the development and use of Darvon may not represent our finest hour.

Acetaminophen is the second part of this less-than-dynamic duo. This substance remains an ever increasingly popular OTC analgesic-antipyretic; new brands are still appearing of the drug alone, e.g., Panadol, and in a host of "cold remedies," "pain killers" (often associated with aspirin), "sinus medicines," etc. The addition of cyanide decreased the usage of at least one brand of acetaminophen for a while over a year ago, but now it seems that these non-aspirin products are being used more than ever. Although it was synthesized in 1877 and first used therapeutically in 1893, it wasn't until the 1950s that it was recognized as the active ingredient of phenacetin and not until 1955 that it was marketed as an OTC medication.

I like to use acetaminophen in children when I need to achieve some fever control and/or pain relief and, in fact, I do not use salicylates in children unless they have a very select disease such as rheumatic fever, juvenile rheumatoid arthritis, Kawasaki's disease or osteoid ostoma. Acetaminophen is quite safe to use in children; unlike aspirin it does not undergo cumulative kinetics. That is, after a non-toxic dose of acetaminophen, the drug is completely metabolized and out of the body by 3 or 4 hours even if the patient is dehydrated and very febrile. It is not easy to cause a "therapeutic misadventure" with acetaminophen as it is in infants who are often given aspirin in too large a dose, in doses too close together, for too long a period of time. Acetaminophen can probably be given to children in much higher dosage than prescribed on the bottle. We give, when indicated, an initial dose of 20-25 mg/kg with subsequent doses of 15-20 mg/kg at 3-4 hour intervals. The toxic dose of acetaminophen in people over 9 or 10 years of age is about 140 mg/kg; the toxic dose in younger patients is not actually known at this time.

Acetaminophen overdose continues to be a big problem in at least two instances: (1) accidental ingestion by preschool children, (2) purposeful ingestion by teenagers and young adults. If my recent experience is any indication, the problem of overdose with acetaminophen and acetaminophen-containing products is increasing. In order to understand the management of this overdose situation a bit of toxicokinetics must be discussed (I love that word!!). About 94% of ingested acetaminophen is conjugated in the liver with glucuronic acid and sulfate and excreted in the urine in a non-toxic form. About 4±% of the acetaminophen is metabolized in the liver, by the hepatic cytochrome P-450 mixed function oxidase system (say that 6 times rapidly!!) to an *active intermediate metabolite*. This metabolite is the bad news part of this whole mess; normally it is detoxified, in the liver, with glutathione and excreted in the urine. However, when 70% of the hepatic glutathione is used up (as in an overdose) this very active, obnoxious metabolite binds covalently to liver macromolecules and causes acute centrilobular liver necrosis. A 70 kilo person who ingests 15.88 grams of acetaminophen acutely will probably use up 70% of hepatic glutathione and have liver injury as a result.

Without a good history, the diagnosis of acetaminophen toxicity is a very difficult one clinically and consists of about 3 phases. In the *first phase* which begins about 6 hours or more after ingestion of the overdose, there is nausea, vomiting, anorexia, diaphoresis, pallor and malaise (you know, I recently learned that not everyone feels like this on Monday morning) — all non-specific of course and not much help diagnostically. Phase I lasts about 12-24 hours. Coma or other evidence of CNS depression does not occur in this phase; if it does, you had better look for co-ingestants like ethanol, barbiturates, tranquilizers, sedatives or other CNS depressants such as our old friend propoxyphene. In this phase liver enzymes do not become abnormal. *In Phase II* the patients often say they feel better but in reality they are worse, i.e., the liver enzymes and serum bilirubin increase, the prothrombin time is prolonged, the liver is enlarged and tender. The majority of patients do not progress beyond this phase. (In acetaminophen overdose, hepatic toxicity is often defined as an SGOT of 1000 IV/l.) *Phase III* can be divided into two subgroups: (1) in the majority of patients there is a resolution of liver function abnormalities to a normal state. The peak of liver enzymes abnormalities is reached in about 72-96 hours and they resolve by 6-8 days; (2) in a very small number of overdose patients there is acute hepatic necrosis and liver failure complete with hepatic encephalopathy and death. Renal failure and cardiomyopathy can also occur. Be careful, renal failure may not be reflected by a rising BUN as urea production can be decreased secondary to hepatic necrosis. Patients surviving this toxic encounter experience no permanent liver sequelae.

The good news is that acetaminophen poisoning is quite treatable if you follow some basic principles such as: (1) *Empty* the stomach by conventional means depending on the consciousness of the patient. (2) *Do not give activated charcoal* if you have reasonable certainty that acetaminophen alone was ingested. The reason for this is really quite simple, i.e., the antidote for this poison is administered orally (at least it is in the United States) and the charcoal will absorb it. (3) Obtain an acetaminophen *blood level* at least 4 hours after ingestion, not before, and plot the result on the Rumack-Matthews acetaminophen overdose nomogram. (4) Obtain baseline lab studies such as CBC, platelets, prothrombin time, bilirubin, BUN, electrolytes, glucose and liver enzymes. (5) Give the antidote N-acetylcysteine (Mucomyst) if indicated. Now there is a catch to all of this — this antidote is not yet approved by the FDA even though it has been used for several years. Supervision for the antidote use can be obtained by calling the Rocky Mountain Poison Control in Denver, Colorado (toll-free 800-525-6115) where you will be entered on their protocol and given instructions.

You might ask if Mucomyst is the only treatment. Well, glutathione would be the perfect thing to use except you can't put it into the liver cells as yet. Methionine and cysteamine have been used but can have severe side effects. N-acetylcysteine which acts as a glutathione substitute

seems to have shown the greatest promise of preventing hepatotoxicity without significant side effects. In this county the antidote is given orally but in Great Britain it is administered intravenously. For the best results, N-acetylcysteine should be given in the first 16 hours post ingestion and becomes less effective as the 24th hour post ingestion is reached.

For reasons that remain unexplained even as we speak, acetaminophen toxicity is considerably less of a problem in preschool children. Very few cases of acetaminophen hepatotoxicity have been reported in this age group in this county. In our experience, at our hospital, we have not had a preschool child with an acetaminophen overdose who had an SGOT $>$ 100. Nevertheless, be cool and use good clinical judgment when confronted with this poison in this age group.

I told you initially that there were three major problems in Darvocet overdose situations: (1) propoxyphene toxicity, (2) acetaminophen poisoning, (3) problems created by the combination of #1 and #2. It is to the latter problem that I wish to speak now. You see, I neglected to tell you that N-acetylcysteine is definitely "barf-city." This stuff smells so awful that when you walk into a room where it is being used and you are not aware of it, you walk gingerly so as to avoid stepping on something foul. It tastes about as bad as it smells and is classically given orally by admixture with Coca-Cola, Fresca, grapefruit juice, etc. in attempt to disguise the taste. It is quite irritating to the stomach with vomiting a likely result. If the patient vomits the oral dose within one hour of administration it needs to be repeated. But what would you do if the patient continues to vomit or is obtunded for any reason, but needs the drug? You would insert a naso-duodenal tube of course. Aha, here is the rub and the point of this entire message. There was something else I didn't tell you; if the patient also ingested a narcotic-like substance along with the acetaminophen (like Darvocet) something confounding can happen to the GI tract. Opiates can remarkably decrease bowel motility to the point of ileus, can increase antral tone, can decrease the absorption of drugs taken orally and more importantly increase the tone of the first portion of the duodenum so remarkably that the passage of a tube into the duodenum may be difficult or impossible as long as 12 hours post ingestion. For this problem I would like to suggest a solution that I have not seen in print. If naloxone is as innocuous as we believe it is, why not give some in an attempt to reverse the spasm caused by the propoxyphene (or other opiates) so that the tube can be passed. It's worth a try!!

There are many important lessons to be learned here, but I believe that uppermost in the minds of those whose task it is to manage overdose patients is to remember that teenagers and young adults typically overdose in a polypharmaceutical fashion and you must look as hard as you can to determine what was consumed. For instance, if the clinical picture suggests a propoxyphene overdose, look for acetaminophen or aspirin overdose as well. If you fail to do this you might be treating one toxin only to have the patient die from another one.

As for me, no narcotics, thank you. I recently read where laughter can release your body's own endorphins and thus relieve pain. My latest research project involves the use of a large feather duster which I apply to the patient's bare feet postoperatively to see if I can relieve pain. The control group watches re-runs of "Leave It To Beaver."

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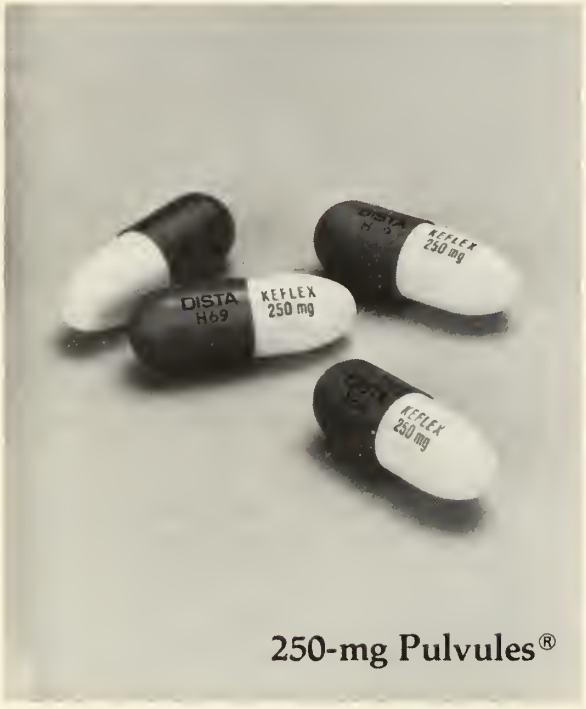
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Cut Off From People

LuVern H. Kunze, Ph.D.

Blindness cuts one off from things. Deafness cuts one off from people.

Helen Keller

Twenty million Americans or one of every ten people are "cut off from people" because their ability to communicate is defective in some way. Some, like Helen Keller, do not perceive what others are saying because of a decrease or absence of hearing. Others have adequate peripheral hearing but cannot understand what they hear because of deficiencies in the central nervous system. Still others lack the ability to express ideas and feelings through speech. The loss or reduction of the ability to communicate results in isolation and a reduced quality of life. The ability to learn is limited for lack of input of information. Opportunities for business and professional success are diminished. Interaction with family and friends is impoverished.

Communicative disabilities need not be accepted as inevitable and irreversible. Many communicative disorders can be treated effectively, particularly if they are identified early. Professionals who help the communicatively handicapped patient have methods for identifying such patients early.

Evaluation and treatment of hearing impaired persons is the responsibility of the audiologist. Evaluation and treatment of individuals having speech and/or language disorders is the responsibility of the speech-language pathologist. To be licensed to practice in North Carolina, these professionals must have earned a masters degree and have completed a one year internship under the supervision of a licensed practicing professional. Nationally, speech-language pathologists and audiologists must meet the same requirements to obtain a Certificate of Clinical Competence from the American Speech-Language-Hearing Association.

There are many kinds of hearing, language, and speech disorders that may limit a person's ability to communicate with others.

Hearing Impairment

Children born with sensorineural hearing impairment are cut off from people more than any other group of communicatively handicapped persons. From birth, they are deprived of the sensory stimulation they need in order to acquire the language skills necessary for learning, communication with others, and economic success.

Early identification of children born with hearing impairment is essential if treatment is to result in the acquisition of acceptable language skills. Children learn to understand and use language in predictable steps with each skill acquired at a particular time during the first five years of life. Skills not acquired during this maximal learning period are learned with greater difficulty at later stages of development. The longer the delay, the more difficult will be the learning process. The child whose hearing impairment is not identified until he is three years of age has lost the most important years of language learning.

Hearing impairment can be identified at birth through the use of auditory brainstem response (ABR) audiometry. This new technique measures electrical activity in the brainstem while sounds are being presented to the patient. A computer identifies both the extent of hearing loss and the location of the disorder causing the hearing loss. Because ABR audiometry does not require the cooperation of the patient, it is ideal for identification of the existence of a hearing impairment in infants, very young children and other hard-to-test individuals. Although complete description of the nature of the hearing loss must await the time when the child can cooperate in behavioral audiologic testing, vital treatment can begin as soon as the loss is identified. Hearing aid amplification and training for the best use of available hearing help the child acquire language skills during the normal learning period. Hearing status should be reevaluated regularly by the audiologist and the otologist to assure that amplification and medical treatment are appropriate. Counseling and training for parents help to assure normal social adjustment. As the hearing impaired child develops, special schooling may be required.

From the Division of Speech and Hearing Disorders, Box 3887, Duke University Medical Center, Durham 27710.

Illustrations by Ernest Craige, M.D.



If periods of hearing loss persist as the child enters school, poor academic performance may result.

The most common type of hearing impoirment in preschool ond primory aged children is the conductive heoring loss resulting from the occumulation of fluid in the middle eor becouse of otitis medio (middle eor infections). Although such o loss is typicolly both mild ond temporory, the child experiences significont difficulty in heoring ond understanding whot others ore soying during periods of infection. It is importont thot medicol treotment of otitis medio toke into occount the impoct of the heoring loss on the child's learning potential. Reseorch hos shown thot frequently recurring eor infections during the longuoge leorning yeors con result in o significont deloy in the ocquisition of longuoge and speech skills. If such periods of heoring loss persist os the child enters school, poor ocodemic performance may result becouse verbolly presented instructions ond informotion are not understood.

Heoring impoirment moy be ocquired ot any oge as the result of troumo or diseose. Exposure to loud noise over a long period of time may produce significont heoring loss. In porticulor jeopordy ore those close to loud music, noisy mochinery or fireorms without ear protection. Heoring loss resulting from noise troumo is irreversible, although it may be relieved portiolly by heoring oid omplificotion.

Reduction in heoring ocuity is common omong senior citizens. As hordening of the arteries progresses with oge, the function of the cochleo (primary orgon of heoring) is diminished becouse of the decreose in the blood supply to the oreo. Typicolly, such deficiencies produce both loss of sensitivity ond reduction in discriminotion skills. Although coreful fitting of o hearing oid is likely to improve ocuity, the potient moy continue to experience difficulty in understonding what is being soid, especiolly in o noise-filled environment.

The tosk of the oudiologist is to identify the hearing loss, to describe the degree of the loss ot frequency levels important to understonding speech, ond to provide informotion required to establish the couse of the loss. After medicol treatment, the oudiologist fits the potient with a heoring aid when oppropriate ond ossists the potient to moke moximol use of ouditory and visuol cues for communicotion.

Childhood Language Disorders

Mony children ore cut off from people becouse their abilities to understond ond/or use longuage ore defective, even though their heoring is normol. Such defects moy be coused by o general delay in psycho-sociol development or may be specific to communicotion skills in o child who is developing normolly in oll other ospects.

Longuoge is o complex system of

symbals used in listening, talking, reading ond writing. Language development in the normal child begins with the acquisition af certain prelanguoge behaviars during infancy, progresses through a predictoble sequence af acquired skills and is completed by the age af five years, except far the expansian af vocabulary that cames with increased educatian and experience.

Pre-language behaviors which must be learned befare languoge can be acquired include looking inta the face af a speaker (three months), turning taward the source of a human vaice (faur manths), babbling and vacal play (four months), motar and vacal responsiveness ta verbal stimulatian by parents (five manths), using shart strings of cansanant-vawel syllables (e.g., ba, daa, me) during vocal play (six manths), stapping activity in response to "na" spaken sharply (six months), and imitating vacalizotians af an adult with same accurocy (eight manths).

A child's understanding af language used by athers (receptive languoge) and his employment of language ta express his desires, needs, ideas, and ematians (expressive language) develap in parallel, with receptive skills appearing a short time befare camparable expressive skills. Acquisition af bath receptive and expressive skills depends on innate patential far language learning and an stimulation and reinforcement by peaple in his enviranment.

After first wards appear (10 to 18 manths), the child's longuoge skills increase ropidly in several areas, including develapment af ideas (cancept formatian); assignment af wards ta abjects, actians, concepts, and emotians (semantics); acquisition af rules gaverning changes in words ta designate tense, number, and case (morphalagy); learning rules governing ward order and sentence structures (syntax); acquiring rules governing interpersanal cammunicatian (pragmatics); and perceptian and productian af saunds and saund sequences for speech (phanalagy and articulation).

Language leorning is nat a process af imitating what has been heard. It is a pracess in which a child develaps rules abaut language that he then uses in generating sentences af his own. At first, his sentences are quite different fram thase used by adults. As he learns the rules, his sentences became like adult sentences.

Children have an inbarn predispasitian far learning language during the first five years af life. Patential far successful treatment af a language disorder is greater if it is identified early to take advantage of this period of heightened learning potential. Porents who are concerned that their child may be delayed in longuage ocquisition frequently postpane seeking professianal help, thinking the child might "autgraw it." Such a delay is very castly far the child who needs treatment, since his ability to compete in sacial and educatianal settings is limited by his inability ta use language effectively. Such a delay is alsa unnecessary, since the speech-language pathalagist is prepared ta differentiate between thase wha will develap narmally and thase wha will need treatment.

The speech-language pathalogist has many tests and ather evaluative pracedures avoilable ta assist in describing the child's capabilities in each area af language utilizatian. A sample of the child's language is carefully analyzed to yield specific infarmation abaut the ideas he is expressing, the words he is using, and the grammar he uses in forming sentences. Treatment plans are designed to imprave the child's function in thase areos in which perfarmance is belaw the level expected af a child of his age.

The task of the speech-language pathalagist is ta structure learning experiences which help the child acquire rules that are cansistent with acceptable adult language usage. Once these rules are learned, the child can generate sentences to express any ideo he wishes and thereby to participate fully in sacial and educatianal situatians.

Aphasia

Aphasia is a language disarder that may be acquired at any age but is usually acquired in adulthood as the result af brain damage secandary ta neuralogical disease (e.g., stroke) ar trauma. Typically, there is a general reductian in language abilities acrass all language pracesses (understonding spaken language, reading, speaking, and writing), althaugh the severity of the deficiency may vary fram ane language pracess to anather.

The aphasic patient experiences a loss ar reductian in available vocabulary. Wards he heors no langer have distinct meaning. He has difficulty recalling wards he needs for self expressian. In general, words that are used mast are mare likely ta be retained ar relearned. Wards having closely assaciated meaning ar words that sound alike are frequently confused. Ward finding capabilities are decreased. The ability to attend to and retain verbal infarmatian is reduced ar lost.

Reading and writing skills may be similarly last or decreased. As visual perceptual skills are impaired, printed and written words lase their symbolic value and became meaningless marks on a page. The inability ta canceptualize written symbols makes writing difficult or impassible. Visual field deficiencies may result in the patient's seeing anly part af what appears in the visual field. He appears to ignare a part af the visual infarmation available. The ability ta attend ta visual stimuli may be reduced. Deficiencies in the perceptian af spatial relatianships create difficulty in fallawing a printed line and in maving fram line ta line.

Articulatian may be defective because the patient recalls imperfectly the motar mavements and mavement sequences required ta pronounce wards correctly. Speech sounds having similar mator mavements may be substituted for one anather.

Number concepts and computational abilities may be impaired.

Aphasia affects every part of the patient's life. The aphasic patient finds himself dependent on his family, friends, and other associates. He may lose control of many aspects of life, with decisions frequently being made for him. His effectiveness in business or professional life may be impaired, sometimes to the point that he must give up a position he has held for many years. His general effectiveness in human interaction is diminished or lost.

The responsibility of the speech-language pathologist is to describe through tests and observation the specifics of the patient's disorder and to plan a treatment program directed toward helping the patient communicate as effectively as possible considering his neurological state.

Voice Disorders

The sound that is used for speech is produced when air forced from the lungs vibrates the vocal folds (vocal cords). When the air supply is insufficient because of reduced lung capacity or when the flow of air across the vocal folds is poorly controlled because of neurological impairment, voice production may be inadequate for intelligible speech production. Unpleasant voice quality or complete loss of voice may result when vocal folds are deformed, when the vocal folds are damaged by a blow, when polyps or nodules (abnormal growths) appear on the vocal folds because of vocal abuse, or when one or both of the vocal folds are paralyzed. Absence of voice results when the larynx containing the vocal folds is surgically removed because of cancer or other major trauma.

The speech-language pathologist participates with the physician in the description and diagnosis of voice disorders. Once medical treatment is complete, the speech-language pathologist may work with the patient to modify vocal production. When vocal sound production is no longer possible, the patient is taught to use alternative methods for sound production, using other organic structures (e.g., the esophagus), surgically created structures, or electronic devices.

Articulation Disorders

The sound produced by vocal fold vibration is modified by movements of the jaw, tongue, lips, and soft palate to produce the sounds of spoken language. Defective speech may result from improperly formed structures (e.g., cleft palate, short soft palate, malformed dental structure, etc.), deficient muscle control (e.g., cerebral palsy, etc.), or incorrectly learned articulatory movement.

Diagnosis of the articulation disorder is the responsibility of the speech-language pathologist. When the articulation disorder involves malformation of structures or deficient muscle control, further evaluation requires the expertise of the physician, the orthodontist and/or dental surgeon. With medical treatment complete, the speech-language pathologist undertakes retraining of the remaining articulation deficiencies, helping the individual attain correct speech production on an habitual basis.

Fluency Disorders

Stuttering (dysfluency) is the fre-

Interaction with family and friends is impoverished.





In particular jeopardy are those close to noisy machinery without ear protection.

quent, apparently uncantrollable pralangatian (audible or silent) af speech saunds and/ar repetition af syllables, wards, or phrases. The dysfluency may be accampanied by unusual mavements af the speech mechanism or other parts af the bady. The stutterer may report feeling tensian, anxiety, fear af speaking ar ather negative ematians and/ar sensatians.

Althaugh stuttering behaviars usually appear first in early childhaad, nat all children wha are dysfluent during the early years af life (three ta five years) will be stutterers. If a dysfluent speech pattern persists for six manths, an evaluation should be saught with a speech-language pathalagist to determine if the pattern observed is that expected af a stutterer ar if it is a prablem that shauld be self correcting.

The evaluation conducted by the speech-language pathalagist pravides a prafile af dysfluent and associated behaviors which will be replaced with fluent behaviars during treatment.

Available Services

The gaal af treatment of those wha are cut off fram peaple because af disorders af hearing, language, and speech is ta help the patient acquire the best cammunicatian system permitted by his physical capabilities. When the disarder has na arganic basis, the results af treatment may be narmal cammunicative functian. When the disarder is the consequence af same organic prablem, the treatment gaal is more effective cammunication even thaugh completely narmal function is nat passible.

Diagnastic and treatment services by speech-language pathalagists and audialagists are available from private practitianers and through many public and private agencies. Services for schaal age children are available in mast public and same private schaals. Services far peaple af all ages are available in mast large haspitals and medical centers. Same public health agencies affer speech-language pathalagy and audialagy services. Some cities have speech and hearing centers separate from ather institutians. Peaple living in ar near cities having majar calleges or universities may be able ta abtain services thraugh professional educatianal pragrams. There are audiolagists and speech-language pathalagists in private practice in mast cities.

Readers wishing ta knaw if a particular practitioner is licensed in Narth Caralina may write the Baard af Examiners far Speech-Language Pathalogists and Audialagists, P.O. Bax 5545, Greensbaro, Narth Caralina 27403 ar call 919/272-1828. Ta determine if a clinician halds the Certificate af Clinical Campetence, write ASHA, 10801 Rackville Pike, Rackville, Maryland 20852 ar call 301/897-5700. Individuals wanting information cancerning speech-language pathalagists ar audialagists practicing in a geagraphic area may cantact either af the above resaurces ar the Narth Caralina Speech, Hearing and Language Assaciatian, 1821 Chapel Hill Raad, Durham, Narth Carolina 27707 or call 919/493-3451.

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There's A Fungus Among Us

Claude S. Burton, M.D., Peter Heald, M.D., and J. Lamar Callaway, M.D.

Mon horbors so mony microorgonisms that the division between infection and hormless colonizotion is often obscure. There ore in foct mony microorgonisms thot are octuolly beneficiol. Very little is known obout the ecology of these orgonisms. The foctors thot moke the difference between colonizotion ond infection ore obscure, though the immune response of the host ond the locol environment (temperoture, moisture, ond elimination of competing bocterio with antibiotics) is thought to be involved. Fungi ore commonly found on surfoces of the humon body yet rorely couse symptoms. It is to the organisms' odvontoge to reside in harmony with the host. If the orgonism troubles the host, then the host will toke steps to eliminote the orgonism.

The dermatophytes ore o group of fungi thot hove odopted themselves to mon. Fifty percent or more of the adults of our species ore found to horbor these fungi yet only o minority will ever have couse to see o physicion or turn to over-the-counter medicotion for relief. However, thot minority of Americons olone will spend over $40,000,000 this yeor to treot fungol dermotitis.

In generol, these fungi live in the most superficiol loyer of skin, the strotum corneum. This, the so-colled horny loyer, is composed lorgely of keratin os ore the hoir ond noils. Keratin, o duroble fibrous protein thot provides o borrier ogoinst the environment, is also the diet of the dermotophytes.

Only when growth of these fungi olerts the host's immune system ore symptoms likely to occur. Once the immune system is alerted, on ollergic reoction to the fungi develops olong with signs ond symptoms of whot we know as fungal dermatitis. Fungol dermatitis is charocterized by itchy, scoly skin, often with redness ond swelling. Fungol dermotitis of the body is commonly referred to os ringworm or tineo corporis (the lotter is the Latin terminology; the Greeks called this herpes). Fungol dermatitis of the foot is known os athlete's foot or tineo pedis. As one con see the nomencloture is geographic — referring to the part of the body involved.

Fungol dermotitis requires o multifoceted treatment. Key ingredients of o successful strotegy include the following: antifungol chemotherapy, treotment of the ollergic reoction, ond modificotion of the environment thot fovors dermatophyte infection. Effective antifungol creams such os miconozole ore useful topicolly ond hove the odvontoge of eliminoting yeast, onother couse of dermatitis thot is often confused with fungol dermotitis. Systemic theropy with such ogents moy be required, especiolly if eliminotion of noil disease is desired. When the ollergic symptoms such os itch ond swelling predominote, corticosteroids are o useful odjunctive therapy. Control of moisture on the feet (frequent sock ond shoe changes, ventiloted footwear, dusting powder) ond in the groin orea (loose clothing, dusting powder) ore essentiol for the treatment of dermotitis in these areos. Despite the best of theropies, relopse is frequent. Like the mistletoe thot finds the ook, the dermotophyte will find those with the right sort of "bork."

Finolly, of prime importonce is on occurote diognosis. It connot be overemphosized thot fungol dermatitis is often misdiognosed and therefore mistreoted. Acknowledging the propensity for fungol dermotitis to mosquerade as other vorieties of dermotitis, Dr. Collawoy hos estoblished the dictum, "If it scales, scrope it." By demonstroting the fungus in scropings of skin obtained eosily ond poinlessly from suspicious roshes one con be certoin of the diognosis. And not oll thot looks like fungal dermotitis is octually due to fungi. We frequently see potients who hove been told they hove "ringworm" who octuolly prove to hove psoriosis, sorcoidosis, or any of a dozen other conditions (including concer) thot require specific theropy. When o "ringworm" does not respond to theropy, seek professionol odvice.



IT'S GETTING TOUGHER FOR NANCY RAY TO BE A MOTHER.

Nancy Ray has multiple sclerosis.

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JUST WHEN YOU'RE STARTING TO LIVE, MS CAN STRIK

EDITORIAL

Impact of Pregnancy on Adolescent Physical, Psychosocial and Socioeconomic Development

Joseph F. Russo, M.D.

THERE are approximately 21 million teenagers in the United States. An estimated 12 million are sexually active. Over one million become pregnant and 600,000 give birth each year. These births account for one-fifth of the total births in the United States.

Five percent of North Carolina's teenagers become pregnant each year of whom more than 24,000 are between 15 and 19 years of age and more than 750 are younger than 15 years. Fifteen percent of these teenagers are pregnant again within one year.

Adolescence is a unique time of physical and psychological growth and development. Since the onset of menarche does not signify the cessation of physical growth and pregnancy increases nutrient needs, we might well expect medical complications to be greater for pregnant adolescents. Since adolescence is a time of emotional growth, the teenager may not be emotionally capable of coping with the many stresses that accompany pregnancy and parenthood. Furthermore, health care providers uniformly feel inadequate when trying to provide services because teenagers are often noncommunicative and noncompliant.

Physical Impact

The obstetrical complications reported most often are maternal mortality, preeclamptic toxemia, anemia, prematurity, low birth weight newborn, and perinatal death. Older adolescents (16-19 years) who receive adequate prenatal care do not experience more obstetrical complications than adult women of the same race, parity, socioeconomic, and marital status.[1] The health of young women prior to conception and the quality of prenatal care during pregnancy influence outcome more significantly than does their age at the time of conception. There is growing concern, however, for the obstetrical outcomes of very young teenagers.

Young age can be a negative factor in regard to the physical readiness for pregnancy. If young women become pregnant before the cessation of their own growth, a dual growth demand is created. Early maturing females (menarche 11.6 years) grow more and for a longer period of time than late maturers (15.2 years) and are at higher risk for poor pregnancy outcomes.[2] Furthermore, the nutritional status and dietary intake of pregnant teenagers are generally poor. About one-half have good diets, one-quarter have fair diets, and the remaining one-quarter have poor diets with deficient intake of calcium, ascorbic acid, vitamin A, protein and iron, and high intake of snack foods and soft drinks. The poorer the patient, the more deficient the diet. The nutritional status of the pregnant teenagers prior to conception and their diet during pregnancy are important determinants of their reproductive performance.[3]

Psychosocial Impact

Adolescence is a time when females develop psychologically as well as physically. Three substages of psychosocial development have been identified — early, middle, and late adolescence.[4] Each substage has specific challenges that need to be negotiated in order to proceed to the next.

Early adolescent females experience the onslaught of puberty with all of the accompanying physiologic, endocrinologic and emotional changes. They are preoccupied with rapid body development and begin to self-explore. Involvement with girlfriends increases, which helps to loosen ties with mother and allows comparison of selves with peers. Dating is limited and usually in groups. The major challenge is the feeling of ambivalence between the emerging need for independence and the lingering need to remain close to mother. If they become pregnant, they usually know little, claim not to have been intimate with the boy, and deny that they are pregnant.

Middle adolescents are the stereotype of self-involved females. They actively seek autonomy from their families. Emotions swing wildly. Peers replace parents. It is a time of promiscuous heterosexual dating. The major challenge is the development of an identity separate from their parents. If pregnancy occurs, it is usually a result of experimentation, romantic fantasizing, or a need to have something of their own rather than as a consequence of intimate feelings toward the boy.

Late adolescents become involved in the resolution of love and work identity commitments. A more stable personality is formed and reality testing is greatly enhanced. They are comfortable with autonomy from their families. Love relationships are more intimate. Future goals and plans are formed. If pregnancy occurs, it is generally a result of needing to strengthen the intimacy they feel for the boy.

From the Department of Obstetrics and Gynecology, East Carolina University School of Medicine, Greenville 27834.

Therefore, the emotional transition from child to adult involves successfully resolving the conflicts arising from dependency versus independency needs and from the establishment of love and work identities. This transition is very stressful. If adolescent females become pregnant, additional challenges are added. They must now develop their role as future mothers and must make adjustments to the physical and emotional changes that accompany pregnancy. If pregnant teens are young, living at home and attending school, they must face parental disappointment and disruption of their families. Often decisions are made for them without consulting them. Therefore, pregnancy at a young age leads to conflict and confusion. It is likely to disrupt the normal process of psychosocial development.

Socioeconomic Impact

Pregnancy is the most often cited cause for young women to discontinue their educations. Mothers who give birth before they are 18 are only half as likely to graduate from high school as those who postpone childbearing until after they turn 20. The impact of pregnancy on education is not simply the result of poverty, low aptitude or lack of interest in learning. The majority of school systems do not deal with the problem of pregnancy in that they either excuse or exclude the young woman by providing home instruction or night school classes. In contrast, young pregnant women in a special educational facility complete school and the majority maintain or improve their grades. The number of years in school has a significant effect upon labor force participation and wage rate. Job experience is not an adequate substitute. Therefore, the fewer are the number of years in school the lower is the wage, and the less likely an individual will be motivated to find work.

The younger the woman at the time of delivery the greater the incidence of poverty and welfare dependency. Among women who deliver a first child at ages 13-15, 16-17, or 18-19 years, there is a 2.6, 2.0, or 1.4 times greater incidence of poverty, respectively, than among those who deliver their first baby after 20 years of age. The mean family income of 1975 of white women who gave birth at 16 or younger was $7,550, which is half the $13,900 earned by families where the mother delayed giving birth until her twenties. The risk of separation and divorce rises as the age of parenting falls. Women who give birth at ages 14-17 are separated or divorced within 15 years at a rate three times the proportion among women who do not begin childbearing until age 20. Furthermore, younger mothers have larger families (50% more children) than do their older counterparts. In 1975, $4.7 billion in Aid to Families with Dependent Children payments to families were made to mothers who gave birth in their teens. Early childbearing results in educational and economic deprivation as well as detrimental sociologic patterns of living. These effects are often perpetuated from one generation to the next.[5]

Many of these detrimental effects of early childbearing can be minimized. Successful programs use an interdisciplinary approach which includes a broad range of personal and health care services. All comprehensive care programs share common service components: communication between community, schools, and health care providers; early diagnosis and referral; continuity of care before, during, and after delivery; ongoing health care education with emphasis on reproduction, contraception, and newborn care; continuous classroom education; and routine inclusion of nutritional and psychological counseling and social work services as part of obstetrical care.

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EDITORIAL

"Hello, Pituitary? — Hypothalamus Calling!"

Francis A. Neelon, M.D.

EONS ago, soon after the first primitive Metazoa began their life on earth as multicellular organisms, the need for intercellular communication must have provided an irresistible stimulus to the evolution of appropriate communication systems. How else could any hungry hydra hunt, without a nerve net to coordinate the recognition and entrapment of its prey? Or the simple slime mold slither to fruition without a hormonal trumpet-call to organize the gathering of individual cells? Today we recognize that evolutionary development has continued along those two main paths, providing animals and man with both a nervous system for highly specific, point-to-point communication and an hormonal system for more diffused and generalized information transfer. Since the common purpose of these systems is to foster cooperation among the components of the organism, it is not too surprising that they should, in turn, interact with each other. Indeed, the study of that interaction forms the basis of the burgeoning young discipline of neuroendocrinology, one of the most exciting frontiers of modern biological science.

Elsewhere in this issue of the *Journal,* Dr. Ontjes brings us up to date regarding two of the latest discoveries in neuroendocrinology: the identification and synthesis of the releasing factors for ACTH (CRF) and for Growth Hormone (GRF). The magnitude of these undertakings is astounding — imagine dissecting and processing half a million sheep hypothalami to garner a few micrograms of purified peptide! But once a trace of the pure material is in hand, the mills of the protein chemists grind miraculously fast — the complete analysis of the GRF seemed to follow almost literally on the heels of the identification of a patient with GRF excess. Almost immediately after analysis came synthesis, so that now there are abundant supplies of synthetic releasing factors ready to be pressed into experimental service as diagnostic reagents or to be used as probes to investigate basic endocrine physiology.

I would bet, however, that the most exciting clinical applications of these new compounds are yet to come. Look at the lessons we have learned from gonadotropin releasing factor (LHRH). It has been in experimental use for less than a decade and only this year achieved approval from the FDA for routine clinical use. In this brief span of time the pioneering studies of Knobil and his colleagues[1] have demonstrated that the beginnings of puberty are encoded in the cyclical secretion of LHRH by the hypothalamus. By mimicking those secretion cycles it is possible to initiate puberty in immature monkeys[1] or, as Crowley and his coworkers have shown, in human beings with hypogonadotropic hypogonadism.[2] On the other hand, sustained infusions of LHRH (or the use of long-lasting synthetic analogues) do not enhance gonadotropin secretion; in fact, they inhibit it. The observation that too much agonist actually impairs gonadotropin output led, in turn, to the use of a long-lived analogue of LHRH to stop the progress of idiopathic precocious puberty in humans.[3] Thus, at least in the case of gonadotropin secretion, we now have the means to stimulate or suppress secretion. This blossoming ability to turn pituitary function on or off almost at will augurs a new era in the therapy of hormone disorders. We can hope that the future holds equally promising uses for CRF and GRF.

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Corporate Restructuring: One Answer to TEFRA's Challenge

Paul M. Wiles

WHEN President Ronald Reagan signed TEFRA, the Tax Equity and Fiscal Responsibility Act, September 3, 1982 the Federal Government sent a clear signal to health care providers. The message: The Federal Government is no longer willing to pay costs of services that hospitals and other providers render to Medicare beneficiaries.

TEFRA, designed to save the government $2.8 billion in 1983 and $5.9 billion by 1985, culminates 17 years of tinkering with the Medicare payment system. By year's end, all Medicare-participating hospitals will have been subject to TEFRA constraints on operating costs per Medicare discharge. Further, nearly one-third of the hospitals will have entered the first year of the new Medicare prospective pricing program, with most of the others following as their new fiscal years begin in 1984.

From a political viewpoint, the Act satisfies taxpayers by reducing the Medicare cost liability without changing the benefit package offered to an increasingly vocal Medicare population. With passage of the Act, the government has told providers of health care to find their own solutions to the problem of inadequate funding. Solutions may include improved productivity and more efficient use of routine ancillary services in meeting patients' needs.

Recently, however, another solution has surfaced, corporate restructuring of nonprofit hospital groups. To understand why this option is being considered, it is important to understand the marketing dynamics facing hospitals today.

Medicare and the Graying of America

The root of the problem is the growing Medicare population, people over the age of 65. While the U.S. population will grow between 1980 and 1990 at an 8½% rate, the over 65 age category will increase at a rate of 21% in this decade, a rate two and a half times faster than the population as a whole. By 1990, the over 65 population will comprise 12.6% of the total U.S. population, up from 11.3% (table 1). This will mean that there will be 5,364,000 additional Medicare beneficiaries in the year 1990.

The significance of these numbers to both Social Security administrators and health providers is that the over 65 population uses hospital care three to eight times more than the under 65 population. In 1980 the under 65 population used 860 days of hospitalization per thousand population, the age category between 65 and 74 used 2,580 patient days, and the 75 and over population used 6,880 patient days per thousand population. The over 65 population, with its growth rate of two and a half times faster than the population as a whole and its higher hospital utilization rates, will be consuming hospitalization resources at rates ten times greater than those persons under the age of 65. This utilization rate clearly presents a cost of care problem for both the Congress and the nation. In the past, Congress has dealt with these problems by adopting laws and regulations that reduce the outflow of dollars to hospitals and other providers. Congress has concentrated on payments to health care providers and has been careful to avoid reducing the scope of services to the beneficiaries of the Medicare program. This is obviously an astute political decision that bodes ill for the future financial viability of institutional health providers.

TABLE 1
U.S. Population (000)

	Total	65 and Over	65 and Over, %
1970	205,052	20,107	9.8
1980	227,658	25,708	11.3
1990	247,000	31,072	12.6

Source: U.S. Bureau of the Census, Current Population Reports, Series P-25, No. 922, "Projections of the Population of the U.S.: 1982 to 2050," U.S. Government Printing Office, Washington, D.C., 1982.

The Growth in Cost Shifting

Since its inception, Medicare has paid hospitals on a cost reimbursement basis. The cost to be reimbursed is derived using a Medicare cost allocation process. This process has consistently produced a growing gap between a hospital's full operating cost and the "allowable cost" paid by Medicare. With the called-for savings in TEFRA, this difference will become even greater. In order to cover these unreimbursed costs, hospitals have traditionally played the role of Robin Hood, that is, by cost shifting these nonpayments from the Medicare system to patients who were sponsored by commercial insurance or who pay their own hospital bills. Table 2 shows that the percent of hospital charges reimbursed to hospitals by the Medicare system has declined from 75.4% in 1974 to 68.7% by 1981. The savings called for by TEFRA are likely to reduce that difference between hospital charges and hospital payments to 60.8% by the year 1985.

The new prospective price system, which became effective October 1, 1983, was established by Public Law 98-

From the Forsyth County Hospital Authority, Inc., 3333 Silas Creek Parkway, Winston-Salem, NC 27103.

TABLE 2
Hospital Charges and Medicare Payments, 1974-1981

Year	Hospital Charges Per Day	Hospital Reimbursement By Medicare	Difference in Dollars	Percent Of Total
1974	$120	$ 90.48	$ 29.52	75.4
1975	145	108.90	36.10	75.1
1976	171	127.40	43.60	74.5
1977	197	144.20	52.80	73.2
1978	225	162.23	62.77	72.1
1979	255	181.56	73.44	71.2
1980	294	204.62	89.38	69.6
1981	334	229.46	$104.54	68.7

Source: Office of Statistics and Data Management, Bureau of Data Management and Strategy, Health Care Financing Administration

21, the Social Security Act Amendments of 1983. The Act requires payment to hospitals on a diagnostically related group basis. While this would seem to be a more equitable method of reimbursing hospitals, the Act calls for "budget neutrality," meaning that payment should be no greater than the payment would have been under the Tax Equity and Fiscal Responsibility Act of 1982. Thus, we can continue to project the Medicare reimbursement shortfall, even under this new revised payment system.

Competition for Other Patients

Other factors facing the hospital provider in the balance of this decade are competition, cost containment, need for alternative delivery systems, and the growth of multi-institutional arrangements. Most of these factors have, at least as a part of their genesis, the Medicare reimbursement problem. There will be growing competition between health providers for the patients who are privately sponsored by commercial health insurance or who are responsible because of the nature of the service for their own health care payments. Traditionally, these patients have borne the Medicare shortfall. If hospitals are not able to compete in a cost-effective way for these patients, little or no cost shifting possibilities will remain. Medicare shortfalls will cause hospitals to be even more seriously underfunded. This underfunding will create a two-tiered medical system in which the aged and poor will be treated in facilities able to produce only the level of care commensurate with the payments from federal or state sources. Privately sponsored patients will be treated in facilities that accept few, if any, Medicare patients, and thus, at a lower cost since there will be no cost shifting burden.

Cost escalation in the health care marketplace is an issue that has demanded great public attention. Industry and business leaders have only recently begun to address the cost of their health care benefit packages. In the coming years they will attempt to find alternative methods of providing high quality medical care to their employees without having to underwrite the ever increasing burden of cost shifting. This will lead industrial and business purchasers of health care services to new forms of delivery mechanisms. The recent rapid growth of ambulatory surgery centers and freestanding emergency or immediate care facilities are two examples where costs are lower than similar hospital services and thus economically more attractive, assuming the quality of care to be equal for the treatment required.

Alternative delivery systems, such as those mentioned above, will also compete to satisfy consumer demand.

The consuming public between the ages of 19 and 64 is already indicating its desire for geographically convenient, noninstitutional care. In addition to surgery and immediate care centers, freestanding birthing and wellness promotion centers will provide needed medical services in nontraditional ways.

And finally, hospitals, in an attempt to meet all of these issues, will find themselves more closely aligned through multi-institutional arrangements. From mergers of two or more health providers, to affiliations of multiple providers, hospitals will join to receive the benefits of economies of scale in purchasing, management specialization and other cost saving programs.

The Restructuring Option

One strategy to deal with these problems or opportunities is restructuring. To understand corporate restructuring one must know how hospitals have been organized and owned over the past 30 to 40 years. Generally, hospitals fall into one of four categories. The largest single group of hospitals is known as private nonprofit hospitals. These organizations are generally membership corporations where the members appoint a board of trustees or serve themselves as a board of trustees of a single hospital provider.

Since 1968 there has been a significant growth of the second group, for-profit hospital corporations. These corporations, many of which are listed on the New York Stock Exchange, own or manage for others up to several hundred hospitals. Each of the corporation hospitals is a profit center directed by an administrator working under centralized corporate controls.

The third type of hospital organization is municipal hospital ownership, found predominantly in the South and inner city sections of major metropolitan areas. These hospitals may be owned by a city or county government and operated either by that government or through legal arrangements such as a lease to a not-for-profit corporation.

And finally, state and federal governments operate various kinds of specialty hospitals; for instance, mental health facilities and public health hospitals.

The common factor among private nonprofit hospitals is that traditionally the board of trustees has had as its sole purpose and function the operation of a single hospital provider within the community. Many institutions recognize that this corporate structure can no longer maintain the hospital's market position within its community. This is why over the past five years a good deal of discussion and action has taken place about corporate restructuring, or as it is sometimes referred to, corporate reorganization.

Corporate restructuring of hospital providers attempts to satisfy all or some of the following objectives:

1) To maintain a single standard of quality medical care to all patients without regard to the patient's financial status or third party payor.
2) To develop multiple capital sources. Without capital funds, it will be impossible for hospitals to replace their facilities and equipment or to fund new technological enhancements or programs. Restructuring,

then, will address itself to all forms of capital generation, philanthropy, new revenue sources, improved debt capacity, and even joint ventures or equity funding.

3) To develop new or additional sources of revenue. With the Federal Government paying less for services rendered to their beneficiaries, and with patients requiring new delivery systems, hospitals are finding it necessary to compete in new markets to generate funds to cover federal nonpayments or to provide new services demanded by patients.
4) To avoid burdensome federal and state regulations. In the past, the Federal Government has used the regulatory process to reduce its payments to hospitals. A number of states have adopted rate setting to control health care costs. A proper restructuring plan will reduce the exposure of the constituent organizations to these regulations, as well as the current health planning regulations.
5) To maximize reimbursement. As regulatory processes become more rigid and reimbursements decline, the organizational structure should capture every lawful dollar of reimbursement for the hospital. Reorganized hospitals find that reimbursement is modestly affected. Any change, however, means that the community bears a smaller cost shifting burden.
6) To maintain a stable governance mechanism. Multicorporate restructuring plans should serve to improve communication, planning, and control of all of the organizations. Generally, overall control is done by one board of trustees through the adoption of systemwide policies, while individual boards are responsible for specific functions, thus enhancing their knowledge base and shortening the lines of communication.

Corporate restructuring, or the legal rearranging of a hospital and its related components, generally takes the form of a foundation, a merger, or a parent holding company.

Hospitals of all sizes across the country have restructured by creating foundations, nonprofit corporations under the Internal Revenue Service Code. Foundations are relatively simple to establish and operate. They meet many of the above objectives of restructuring.

The Benefits of Foundations

Foundations have as their principal objective the creation of additional funds through philanthropy. By being separately incorporated they can shelter philanthropic funds from offsets in reimbursement or from rate setters. Through their own forces or subsidiaries they may also operate activities which under reasonable circumstances would be considered normal hospital businesses. These services may include collection of delinquent hospital accounts, physician billing services, the operation of the hospital's snack shop, and other services. Funds raised by the foundation, either through philanthropy or services, can then be contributed to the hospital so they will have minimum adverse impact on reimbursement.

Hospitals use two types of foundations when restructuring. The first is a related foundation (figure 1), where the



Figure 1. *Related foundation.*

board of trustees of the foundation is controlled, generally through appointment power, by the hospital's board of trustees. A related foundation must contribute funds exclusively to the hospital.

The second type of foundation, which is not used as often in restructuring, is an unrelated foundation (figure 2). This kind of foundation remains independent of the hospital and can use its funds for any charitable endeavor. In order to maintain its nonprofit status with the IRS, it is held to a much higher standard of charitable giving.

Foundations pose some challenges for hospital administrators. Related foundations may be vulnerable when assets are consolidated. Regulators or rate setters could consider the foundation's assets the same as the assets of the hospital and thus offset or reduce hospital reimbursements.

A hospital organization with an unrelated foundation has its own problem — two independent boards of trustees. Coordinated governance becomes difficult.

The Parent Holding Company

The ultimate form of corporate reorganization is known as the parent holding company (figure 3), an entity resembling a financial or bank holding company.

The parent holding company most nearly meets all of the six objectives of corporate restructuring. Most important, it allows for flexible responses to the changing health care environment while sheltering non-hospital or non-provider activities from regulators and rate setters. Of course, it still provides coordinated governance and management.

Under a parent holding company, the hospital becomes a subsidiary to the parent corporation. In most cases, both the parent company and the hospital subsidiary are nonprofit organizations. The parent company is responsible for setting corporate-wide policy. It may have other subsidiary organizations both within the health care area and outside, such as proprietary businesses.

The parent company governs through the appointment of boards of trustees or boards of directors at each of the subsidiaries. The board sets financial goals for each subsidiary and is the only body that can amend the articles of incorporation or bylaws of subsidiary corporations. Too, trustees are responsible for long range planning and development of lines of business within the entire corporate structure.

Reorganization experts generally consider the parent holding company the superior form of corporate reorganization because it offers the benefits of control of the



Figure 2. *Unrelated foundation.*

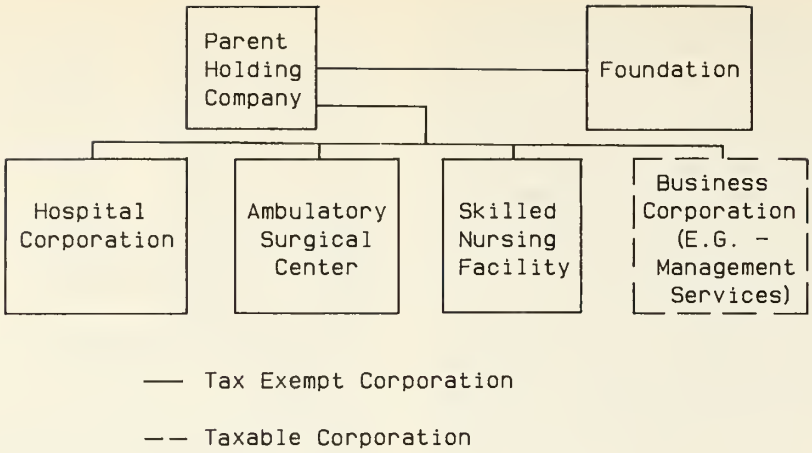


Figure 3. *Parent holding company.*

organization without the liability of consolidation of financial resources in a health care provider. When the balance sheet is consolidated at the parent holding company, the asset and revenue resources are unavailable for offsets by third party payors — the parent holding company is not a direct health care provider itself. Revenues generated in subsidiaries are also sheltered from offsets by federal regulators. In order for the regulators to change this situation, they will have to attack an entire body of corporate law, affecting not only health care holding companies, but also many proprietary corporations that have wholly owned corporate subsidiaries.

After subsidiaries pay their appropriate taxes they can dividend their profits to the nonprofit parent company which in turn can use those profits for the shortfall in Medicare reimbursement to its hospital subsidiaries. The result is a reduction in the cost shifting burden to the community, and consequently, lower charges. The hospital becomes more competitive with providers who are not required to provide care through the Medicare Program.

Involving the Medical Staff

Medical staffs of hospitals should be involved in the restructuring process with the administration of the hospital and its trustees. Generally, the staff should support a restructuring program because, if successful, the hospital will be better able to provide a single level of high quality medical care regardless of the patient's financial sponsor. This, of course, is the objective of physicians in delivering their own health care.

One danger of corporate restructuring, however, is that the hospital and its medical staff may find themselves in direct competition. This situation can usually be avoided through open and frank discussions about the needs of the hospital and the physicians. Enlightened hospital management will recognize the futility of direct head-to-head competition with its medical staff and will attempt to build mutually satisfactory arrangements to provide needed health care services in the community without confrontations with the medical staff.

A Complex Solution for Complex Problems

The need for corporate restructuring arises from complex marketing, regulatory and financial needs. The process of restructuring is also complex in its legal and accounting design as well as in its operation. For certain hospital systems, however, restructuring deserves careful consideration of the issues and the potential solutions it offers.

Medicaid Payments for Nursing Home Services in North Carolina

C. Wayne Stallings

THE decade of the 1970s witnessed an explosion in the number of persons receiving long term nursing care in North Carolina. In 1970 there were only 8,265 nursing home beds in our state. By 1982 the number of beds had increased to 21,034 divided into two distinct levels of care: Skilled Nursing Facilities (SNF), which provide intensive convalescent services, and Intermediate Care Facilities (ICF), which provide less intense service to patients whose physical condition, though reasonably good, requires them to receive continual monitoring and physical support that cannot be provided at home. Fifty-seven percent of the nursing home beds are licensed to provide intermediate care.

There are several reasons for the large growth in nursing services. First, because modern medicine has made it possible for us to live longer, an ever growing proportion of our population is reaching the age where nursing care is likely to be needed. The vast majority (87%) of those who receive institutional nursing care are elderly persons, suffering the effects of serious age-related debilitating illnesses such as strokes, broken bones, diabetes, Alzheimer's disease and the like. The typical nursing home patient is 75 years of age. In 1970 North Carolina had 412,038 citizens over 65 (8.1% of the population). By 1980 this number had swelled to 601,831 (10.2% of our population of 5,881,766). As the number of elderly candidates for nursing care grew, the demand for institutional nursing care also grew. Demographic projections tell us that this growth will continue well into the next century.

Second, changes in family structure and size have made it more difficult for the elderly to convalesce at home. Many nursing home residents have no close relatives. Some have children who are themselves elderly, or nearly so. An 85-year-old woman's children are likely to be in their 60s. Family members may live very far away from their elderly relative, having moved from their hometown or county to get good jobs. Extended families are smaller because of the trend toward fewer children, so the number of persons available to share the financial and physical burden of caring for an elderly relative needing convalescent care is smaller than in the past. In most younger households all the adult members are employed outside the home, leaving no one to care for an elderly relative should it become necessary. Finally, many nursing home patients have very complex medical problems that untrained family members are unable to treat adequately in the home and home health services in the community may not be readily available or affordable.

Despite the limitations on family and home care, however, a very small percentage of the elderly actually require institutional nursing services. Only about 5% of the elderly received care in a nursing home in 1980 although 39% were ill enough to require hospitalization. Clearly, family and friends still play a large role in helping the elderly recover from serious illness.

Third, in our view the most important cause for the expansion of institutional nursing care has been the emergence and growth of public financing through the Medicaid and, to a lesser extent, the Medicare programs. Close to 90% of all nursing care is paid for by these two programs, with the great majority being financed by Medicaid.

Medicare is the publically supported health care insurance program for the elderly and disabled that began in 1965. The goal of Medicare is to relieve the elderly and disabled of the excessive financial burdens of serious illness. Following traditional health insurance patterns, Medicare focuses its attention on the costs of acute care received in hospitals. Eligible persons may also pay an additional premium to receive Medicare coverage for physician care and similar outpatient services. However, Medicare will support only a limited amount of nursing care in a Skilled Nursing Facility. After 100 days in a nursing home the patient must pay the bill from his own resources if he needs further care. If the patient needs intermediate care rather than skilled care Medicare pays nothing.

This limited coverage of nursing home care by Medicare has forced the Medicaid program to shoulder the lions' share of the cost. The Medicaid program was instituted by the Congress in 1965 to provide the poor with access to medical and health care services. Unlike Medicare, which is available to Social Security recipients regardless of their income, Medicaid recipients must be virtually destitute to qualify. Persons receiving cash assistance from programs such as Aid for Dependent Children or Supplemental Security Income are usually automatically eligible for Medicaid benefits. In addition, in North Carolina we permit persons who are not receiving cash assistance to become eligible for Medicaid benefits when their outlays for medical and health care services reduce their financial resources below the poverty level. These persons are called the "medically needy."

From the North Carolina Division of Medical Assistance, Department of Human Resources, 410 N. Boylan Avenue, Raleigh 27603.

Institutional nursing care services have been supported by the Medicaid program since its inception; however, the Program has never imposed the strict limits on coverage of these services that Medicare does. Rather, Medicaid has always paid for an unlimited number of days of care if they were medically justified. Medicaid thereby has become the financial "safety net" for those elderly and disabled persons who need nursing care but haven't the financial resources to pay for it. The financial burden of nursing care that Medicare avoids very often falls upon Medicaid, because relatively few of the elderly and disabled pensioners in our state have the money to pay for the expensive medical and nursing care they need for the full duration of a spell of severe illness and subsequent convalescence.

The North Carolina Medicaid program began paying for skilled nursing care in 1970. Intermediate care was added in 1974 in an effort to reduce the cost per day of care for those persons who still needed nursing service, but at a less intense level than that provided in a skilled facility. Figures 1 and 2 depict the very substantial growth in both the number and cost of nursing care days of service paid for by Medicaid since its inception. From a modest beginning of $16.5 million in 1971, the first full year in which Medicaid services were offered in North Carolina, the program grew elevenfold to 1983's expenditures of $181.2 million. In the coming year we expect to exceed $200 million in outlays for nursing home services.

The ICF program that was introduced in 1974 to contain cost had, by 1976, grown to be larger than the SNF program and has remained so until the current year. Figure 1 shows how the introduction of ICF care did slow, and for two years actually reverse, the growth in the number of SNF days of care purchased by the Medicaid program. This gain was quickly offset by the extremely rapid growth in the number of ICF days of care and the steep inflation in the daily cost of care that struck in the late 1970s (see figure 3).

These growth trends indicate the massive investment in nursing homes that was occurring in the middle and late

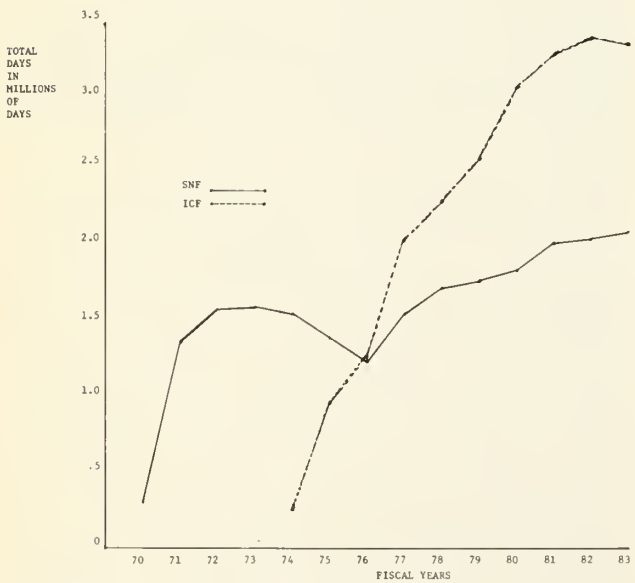


Figure 1. *Growth in the number of nursing care days paid for by Medicaid — 1970-1983.*

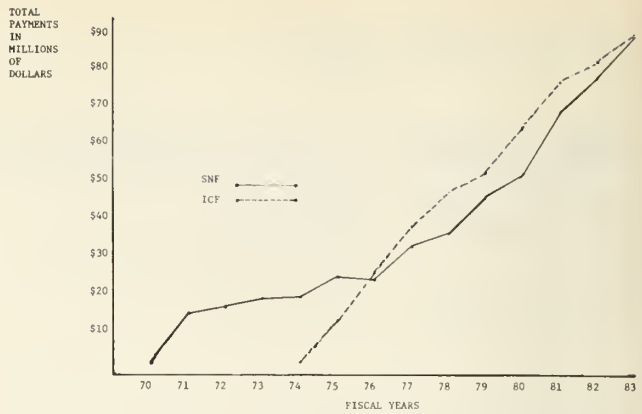


Figure 2. *Growth in Medicaid payments for nursing care — 1970-1983.*

1970s. The large, but formerly latent, demand for nursing services combined with the steady funding source in the Medicaid program to create very attractive investment opportunities that rapidly drew capital into the industry. Nursing home chains, both large and small, sprang into existence. Competition for labor and materials among health care institutions (including both nursing homes and hospitals) intensified, driving up per diem costs at the same time that the number of beds was increasing.

The methods for determining how much Medicare and Medicaid would pay nursing homes for their services exacerbated these inflationary pressures. In its early years Medicare adopted the philosophy that it would pay hospitals and nursing homes only their actual costs incurred in providing care to Medicare patients. Medicaid programs generally followed this lead. At the time this approach seemed conservative. The charges of nursing homes and hospitals were generally set above the cost of care to return a profit or surplus. Paying only cost was cheaper. For a time, when the Medicare proportion of the total days of care provided in hospitals and nursing homes was relatively small, this approach made sense. Market forces, i.e., the unwillingness of private patients to pay excessive charges from these institutions, could be relied upon to keep costs reasonable.

Health care market conditions shifted rapidly in the early

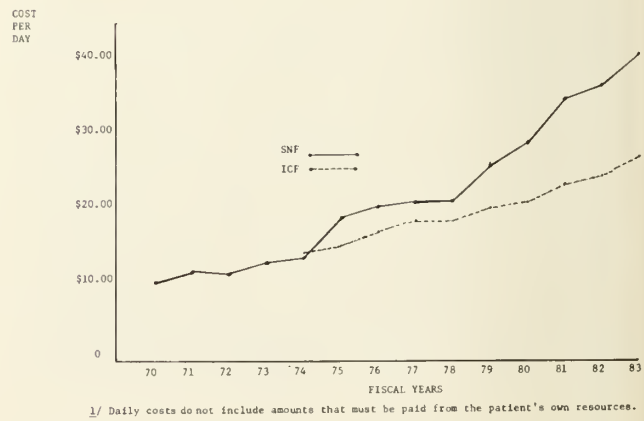


Figure 3. *Growth in daily cost of nursing home services — 1970-1983.*[1]

1970s, however, as a growing proportion of patients turned to Medicare, Medicaid and other health insurance programs to pay for their care. In North Carolina today, Medicare and Medicaid pay for about half of the days of care in hospitals and nearly 90% of the care in nursing homes. With this shift in payment responsibilities from the individual patient to public programs, market pressure to contain costs evaporated. The availability of Medicare and Medicaid funds to finance care enabled many more patients to avail themselves of scarce health care resources, and consequently the prices of these resources increased rapidly. Cost-based reimbursement allowed these large increases in the cost of care to be passed through directly to the taxpayers.

The entrepreneurial environment produced in the nursing home industry by the rapid growth in facilities combined with cost-based reimbursement to foster a variety of financial abuses aimed at maximizing short term profits. Facilities were sold and resold among related parties to pyramid capital costs that could be passed on to Medicare and Medicaid. Inflated lease back arrangements for buildings and equipment were created with similar intent. Mortgages were refinanced frequently increasing interest costs to the public while providing cash windfalls to the mortgagee. Lucrative contracts were signed among related persons to acquire management service of dubious value but at great price. All these abuses contributed to the inflationary spiral in nursing home costs. And, while they did not characterize the industry as a whole, they nevertheless were sufficiently prominent to attract the attention of public officials in our state.

The response of North Carolina policy makers to the rapid increases in the cost of nursing care began to take shape in 1976. At that time the General Assembly declared a freeze on nursing home rates that was to remain in effect until a new method for determining those rates could be implemented. This new method of payment was to cast aside the reasonable cost "pass-through" form of reimbursement inherited from Medicare in order to contain costs.

Pursuant to the 1976 legislation, the Department of Human Resources enacted a prospective reimbursement plan in 1977. The plan was called "prospective" because it set payment levels in advance of services being provided. Under reasonable cost reimbursement final payment levels could not be determined until after services had been provided and actual costs were ascertained. This was called "retrospective" reimbursement. The initial prospective reimbursement plan remained in effect with some modification until January 1980 when the current plan became effective.

The current reimbursement plan for nursing services attempts to achieve three goals:

(1) To support good patient care.
(2) To contain all costs, but particularly administrative and property costs, within reasonable bounds.
(3) To permit a reasonable profit to investors but eliminate financial manipulations that produce excessive profits.

To achieve these goals, the plan contains several unique features that will be described in the following paragraphs.

The current plan sets a reimbursement rate for each nursing home for each level of care. We currently enroll 39 facilities that provide only skilled nursing care and 65 that provide only intermediate care. Each of these facilities has one rate. We also enroll 123 facilities that provide both skilled and intermediate care. These facilities have two rates, one for each level of care.

The rates are based upon the actual reasonable costs incurred by the nursing homes in the year 1978. Homes that have begun operations since 1978 have rates based on their costs in the year they became active. We have been using the cost data from 1978 as the basis for the rates since the inception of the current plan in 1980. The purpose in using the same base for so many years is to establish consistent expectations among nursing home operators about their financial future. This stability enables them to make the long term investments in plant and services needed to improve patient care. It also builds the confidence investors need to overcome the excessive concentration on short term profits that brought on the abuses of the middle 1970s. As we enter our fifth year under the current plan we have seen a growing stability in the nursing home industry in North Carolina that is proving beneficial to patient care.

Each nursing home's rate is divided into two parts, one part to pay for direct patient care services such as nursing care, food service, laundry and linens and various therapies (called the "direct" cost rate), and a second rate to cover property related costs (depreciation, interest, leases, maintenance) and administrative overhead (called the "indirect" cost rate). Although these two components of the total rate are based on 1978 cost data, they are computed separately and affect reimbursement in quite different ways.

To compute these rates 1978 costs for SNF services and ICF services were separated. Next the per diem direct and indirect costs for each nursing home were computed. These per diem costs were then ranked separately from the lowest to the highest. (See table 1 for an example.)

After ranking the direct costs, the 75th percentile of cost was identified. We established this amount as the maximum cost we would allow as a basis for future rates. Each nursing home was given a direct patient care rate based on its actual direct cost in 1978 or the maximum allowable cost (75th percentile of cost), whichever was lower. The per diem direct cost for each home was then adjusted upward by 10% to encourage spending on direct patient care services. This adjustment provided each nursing home with additional funds that could be used to enrich nursing services, patient diets, patient activities, social services and therapy. We believe these additional funds have gone a long way toward fostering the favorable quality of nursing care that patients in this state receive. We know, for example, that most nursing homes now employ far more nurses and nursing aides than the minimum state licensing standards require.

In the indirect per diem cost ranking we identified the 60th percentile of cost (see table 1). This amount became the basis for the indirect rate for all nursing homes regardless of their actual cost. Thus, whereas each nursing home was assigned its own unique direct rate based on its 1978 direct costs, all homes supplying a particular level of care

TABLE 1
Sample Arrays of 1978 Per Diem Cost

Provider	1978 Per Diem Direct Cost	Provider	1978 Per Diem Indirect Cost
	Skilled Nursing Facilities		
Home A	$21.10	Home B	$10.90
Home B	*20.89 75th Percentile*	Home C	10.80
Home C	20.18	Home E	*10.45 60th Percentile*
Home D	20.04	Home A	9.50
Home E	19.50	Home D	8.90
	Intermediate Care Facilities		
Home J	$15.06	Home L	$9.10
Home K	*14.41 75th Percentile*	Home M	9.02
Home L	13.80	Home K	*8.94 60th Percentile*
Home M	13.20	Home N	8.50
Home N	12.90	Home j	8.26

(SNF or lCF) were given the same indirect rate.

Both the adjusted direct costs and the indirect costs from 1978 are adjusted for inflation that has occurred since 1978 to establish the rate that will apply in a given year. To make this adjustment we use inflation factors that reflect the change in prices actually being experienced in the nursing home industry rather than some broad and imprecise measure such as the Consumer Price Index. In fact we even develop separate inflation adjustment factors for the direct and indirect rates because a large portion of indirect costs are fixed, such as building depreciation and mortgage interest, and therefore deserve no inflation adjustment. Table 2 lists the inflation factors that have been used to adjust the 1978 costs to 1982-83 fiscal year levels. Table 3 shows how a nursing home rate is computed using these factors.

We pay the computed rates to each nursing home for an entire year. At the end of that year each home must file an extensive report detailing its actual costs incurred during the year by the type of cost (e.g., salaries, materials) and service area (e.g., nursing, food service, administration). Using these reports we compare the actual costs expended on direct patient care services by each home with its direct rate. If a home's direct expenditures fall below the direct rate, the unexpended funds must be paid back to the Medicaid program. This feature of our reimbursement plan helps ensure that the funds provided by the program for vital patient care services are not directed to other purposes. The patients get the benefit.

We also compare actual indirect costs with the indirect rate. This comparison is made for information purposes only, however, because we permit each provider to retain all the indirect rate regardless of its actual costs. Thus, a home whose indirect costs exceed the indirect rate loses money. A home whose costs fall below the rate makes a profit. Each provider must earn its profit by keeping its property and administrative costs within reasonable bounds. It cannot profit by reducing vital patient care services.

We believe that our current reimbursement system for institutional nursing care has produced the favorable results it intended. First, in a period of high inflation, the increase in nursing home rates in North Carolina has been held below national inflation (see table 2). Second, we have given needed financial stability to an industry that had been buffeted by frequent shifts in reimbursement policy. Consequently, we have seen many of the abusive practices used in the past to maximize short term profits dwindle away. Instead, we have established a funding base that permits reasonable long term profits. In FY 1982 the average nursing home profit margin was a modest 6%. Third, and most important, vital patient care services have been maintained and enhanced.

As we look to the future of nursing care reimbursement we face many challenges. The need for care seems to be expanding at a faster rate than we can afford. We must find less expensive ways to get the job done.

For the near future, institutional care in nursing homes will remain the principal means for delivering nursing care. But, an increasing emphasis will be placed on home and community-based alternatives that enable patients to con-

Table 2
Long Term Care Inflation Allowances Compared to Broad Measures of Inflation

	Nursing Home Inflation Rates				
	Direct %	Indirect %	Weighted Average	CPI %	CPI Medical Care Component
1978 Base					
1979	9.1	9.1	9.1	11.8	9.2
1980	8.0	8.0	8.0	12.7	11.0
1981	9.9	7.0	8.9	11.0	11.5
1982	8.2	5.8	7.3	5.0	11.4
1983	6.7	5.0	6.1	2.4	8.4
Cumulative % Increase	49.0	40.0	46.0	50.0	63.0

Table 3
Examples of Nursing Home Rate Calculations

	Direct	Indirect	Total
Nursing Home C. (SNF)			
1978 Base	$20.18	$10.45	
Patient Care Incentive	×1.10	×1.19	
Adjusted Base	$22.20	$10.45	$32.65
Inflation Adjustments			
1978 to 1979	×1.091	×1.091	
1979 to 1980	×1.080	×1.080	
1980 to 1981	×1.099	×1.070	
1981 to 1982	×1.082	×1.058	
1982 to 1983	×1.067	×1.050	
1982-1983 Rate	$33.19	$14.63	$47.82
Nursing Home J. (ICF)			
1978 Base	$14.41	$ 8.94	
Patient Care Incentive	×1.10	×1.00	
Adjusted Base	$15.85	$8.94	
Inflation Adjustments			
1978 to 1979	×1.091	×1.091	
1979 to 1980	×1.080	×1.080	
1980 to 1981	×1.099	×1.070	
1981 to 1982	×1.082	×1.058	
1982 to 1983	×1.067	×1.050	
1982-1983 Rate	$23.70	$12.51	$36.21

valesce at home. New organizational forms and service delivery methods will have to be developed, perhaps combining professional services with the assistance of family, friends and volunteers. With these new forms new reimbursement techniques will have to be evolved to finance adequate services while discouraging waste.

In nursing home reimbursement itself, we can also expect changes. In the near term we will probably have to update our rate base from 1978 costs to costs in a more recent year because, as time passes, changes in nursing home service delivery are pushing the 1978 cost structure toward obsolescence. When we make the change, adjustments in the direct/indirect rate composition and computation methods will probably be necessary to protect the achievements of the current plan.

Over the longer term we will have to consider some difficult issues such as more direct links between individual patient conditions and reimbursement rates, the extended family's financial responsibility for the care of elderly relatives, and the possibility of encouraging a measure of price competition among similar nursing homes.

Whatever the result of these challenges we have learned that a well conceived reimbursement policy is a powerful tool not only to limit expenses, but also to encourage the rational use of financial resources and high quality patient care. We hope to build upon this knowledge in meeting these future challenges.



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Babies Hospital, 1920-1978

Lockert B. Mason, M.D.

BABIES Hospital in New Hanover County opened its doors in 1920 to serve sick infants and children without regard to ability to pay or county of residence. It began with twenty-two beds and enlarged over the years to sixty beds. It ceased operation in 1978.

The hospital was not the earliest concern for the needs of sick children in southeastern North Carolina. In the late 19th and early 20th centuries the salubrious effect of seabreezes was widely acclaimed. In 1896, James Sprunt, author and philanthropist, stated, "It is a matter of fact that salt sea air will often do more good to a sick, puny child than any of the medical remedies in the pharmacopoeia. Many anxious, worn out mothers have had reason to bless Captain Harper as the means under providence of restoring to health their sick or feeble little ones. A beloved physician has often said that daily trips from Wilmington to Southport are even more beneficial to sick children than a residence on the seashore. The gliding motion of the boat soothes them, the clear fresh air of the river invigorates and strengthens them, and the entire freedom from dust and grime which is so disagreeable and hurtful on railroad journeys brings grateful sensations of cleanliness and comfort to young and old alike."[1]

The reference is to the steamer *Wilmington* which made daily trips from Wilmington down the Cape Fear River to Southport, a distance of about 20 miles, leaving at 10 A.M. and returning at 5 P.M. At that time Captain John Harper had completed more than 13,000 trips between Wilmington and Southport and was considered the most popular man in Wilmington (figure 1).[2] The *Wilmington* was built in 1882, and was 139 feet long, could carry 650 passengers, and had a top speed of 17 miles per hour. Sick babies from the up country and the city were taken on the trip to benefit from the sea breezes. About 1910 the trips were continued on the Steamer *Southport*. Shortly thereafter, the custom was discontinued as "all too often these little sufferers became an unwelcome nuisance."[3] Evidently some of the children died on the trip and this was the nature of the nuisance.

The need for special care for infants was greatest during the summer months because of the prevalence of diarrhea and dehydration caused by lack of screens, abundance of flies, and inadequate refrigeration of milk which was fed after the infant was weaned.

In 1915, Dr. J. Buren Sidbury established practice in Wilmington after postgraduate training in pediatrics in New York City. Within a year his practice had grown to the extent that he limited it entirely to pediatrics, thus becoming the second pediatrician in North Carolina following Dr. Albert S. Root of Raleigh. In the spring of 1920, Dr. Sidbury purchased a large wooden cottage and surrounding land overlooking Wrightsville Sound and Wrightsville Beach (figure 2). He appealed to the citizens of the area to assist in furnishing the hospital to provide care for sick infants and children regardless of county of residence and ability to pay. In his appeal he cited the success of seaside resort hospitals for the treatment of sick babies and children in Atlantic City, Hugenot, New York, Cape May and Virginia Beach. Individual contributions from one dollar to one thousand dollars totaled $3,773.39 in the first year. In addition, there were gifts of furniture for a nurses' office, five cots, half bushel of potatoes, two cans of disinfectant and fly killer, two weeks supply of milk, linen, flat silver and dishes, baby carriages and go-cart, chiffonier and cribs. (The cost of endowing a charity bed for the summer was $200.)

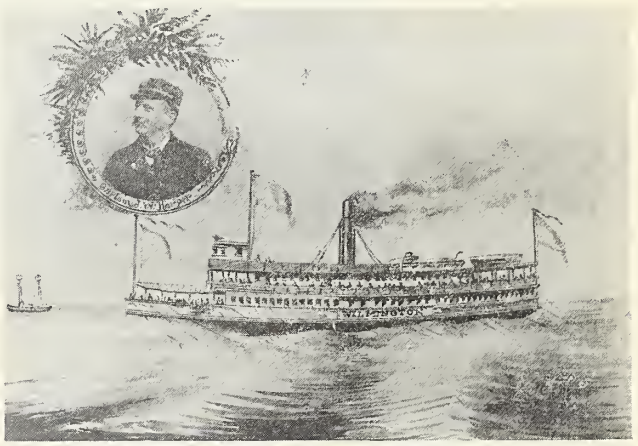


Figure 1. *The steamer* Wilmington: *Captain Harper, insert.*

The Babies Hospital opened on June 6, 1920. It contained twenty-two beds, seven of which were designated for charity patients. During the first season there were 83 patients, 14 of whom were charity and the per diem cost was $3.42. Within the hospital was a milk station capable of preparing any prescribed scientific feeding. In addition to serving the patients in the hospital this milk service was made available for babies in the surrounding area, a great convenience to families visiting Wrightsville Beach and Wrightsville Sound. During the first summer 1,200 feedings were prepared for babies outside the hospital. The hospital closed at the end of the season and continued to operate only in the summer months until 1939.

In 1921, an annex to include eight additional beds was

From the Department of Surgery, New Hanover Memorial Hospital and the Department of Surgery, University of North Carolina School of Medicine.



Figure 2. *Original Babies Hospital.*

added. In 1924, a second annex was added to include a dining room. Dr. Sidbury recognized the importance of the psychological support of having the mother stay with the baby and accommodations for mothers in the rooms with their children was arranged in 1922 and continued throughout the existence of the hospital.

On Sunday, May 29, 1927 the hospital was demolished by fire and the nine patients were transferred to the James Walker Memorial Hospital in Wilmington. At that time the counties adjacent to New Hanover made no provision for hospital care of indigent children and the James Walker Memorial Hospital was not supposed to accept charity cases from outside New Hanover County. For this reason it was urgent that an alternative arrangement be made. A few hours after the fire the Board of Directors of the Babies Hospital met and decided to resume operations in another cottage on Wrightsville Sound which had been made available for a dollar for the remainder of the season through the generosity of the Murchison Bank and its president, Mr. J. V. Grainger. On September 23, 1927, a certificate of incorporation was amended to meet the needs of a new hospital as a nonprofit stock corporation. In December 1927, a contract was let for a two story fireproof hospital which opened on June 15, 1928, having been constructed with funds from insurance on the old building and from donations by public subscriptions (figure 3).

Beginning in 1939, the hospital remained open year round. Hurricane Hazel struck October 15, 1954 at high tide. Buses at the back door were prepared to remove the patients when necessary. Dr. Sidbury delayed the decision because he believed the building to be one of the safest in New Hanover County. The Atlantic Ocean completely covered Wrightsville Beach and reached the first step of the front porch of the hospital. The waters then receded and evacuation was not necessary. The hospital served temporarily as a headquarters for the Red Cross, Salvation Army,



Figure 3. *Babies Hospital 1928.*

and other rescue workers.

In 1954, there were 1969 admissions and an appeal was made for contributions to enlarge the hospital adding more beds and two new operating rooms. The addition of a third floor, which was made possible by a large contribution from Mrs. Jessie Kenan Wise and donations by other friends, was dedicated on July 8, 1956.

The Willie Daniel Sidbury Nurses Home was constructed behind the main building in 1955, a gift of Dr. Sidbury as a memorial to his wife.

Again through the generosity of Mrs. Jessie Kenan Wise another building was constructed on the property to house a pediatric research center and was dedicated in December 1962. Dr. Daniel C. Darrow was the first director of the research center and continued his life-long study of fluid and electrolyte balance. Following his death in 1965 it became advisable to change direction of the research and it became a marine biomedical research laboratory under the direction of Dr. Ralph Brauer with the cooperation of the deans of Duke University Medical School, Bowman Gray School of Medicine, and the University of North Carolina School of Medicine. In 1971 the facility was donated to the University of North Carolina at Wilmington and continues as the Institute for Marine Biomedical Research.

Realizing the need for nurses with special training in the problems of sick children Dr. Sidbury (figure 4) began to offer training to outstanding graduates of the James Walker Nursing School in 1928. Many of these nurses became pediatric supervisors in hospitals of North and South Carolina. From 1942 until 1967 the hospital conducted a nurses training program to which senior student nurses from hospitals throughout the state were sent for three months of pediatric training.

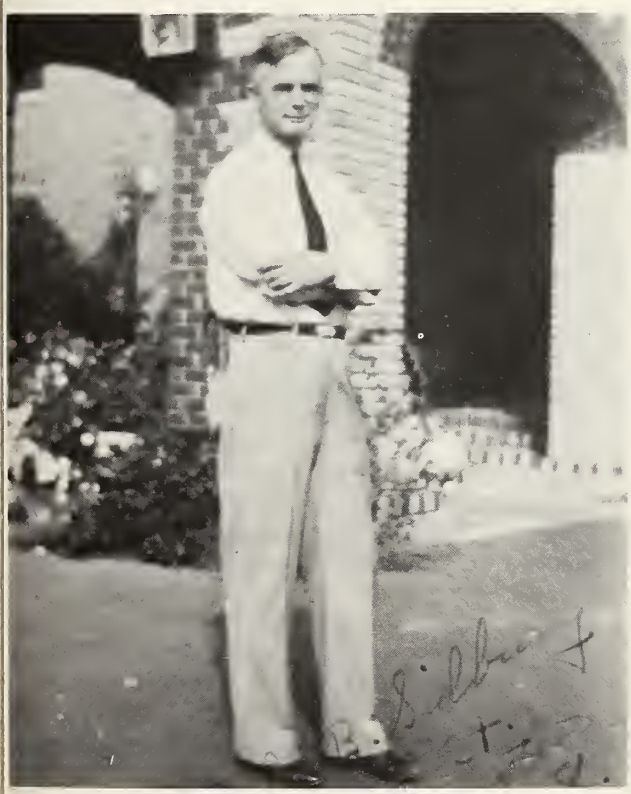


Figure 4. *Dr. Sidbury 1928.*

An approved pediatric residency was conducted until about 1965. A number of pediatricians now practicing in North Carolina and elsewhere trained at Babies Hospital. After the residency was discontinued an elective rotation was offered to interns from James Walker Memorial Hospital in Wilmington.

The year 1967 was of greatest usage with average daily census of 42 patients of which 2.8% were free days according to the Duke Endowment definition. In the previous and following years free days were 7.7% and 7.8%. The aberration in 1967 is not explained. Progress in prevention and treatment of children's diseases replaced the efficacious sea breezes and diminished the necessity for hospitalization of infants and children. Average daily census declined to 17 in 1977, the last full year of operation. It became evident that the need for a pediatric hospital was diminished and the Board of Directors elected to close the hospital in mid 1978. In its fifty-eight years of existence no tax monies were used in the construction or operation of Babies Hospital. Thus ended an era in which a nonprofit hospital for treatment of private and indigent patients could be built and operated without assistance of tax funds. For the first fifty years there was no Medicaid to help pay for the charity patient. The Duke Endowment gave $1 a day for each day of indigent care for many years. In the depression of the 1930s this was approximately twenty-five per cent of the per diem cost. In 1955 the Ford Foundation gave an unsolicited $40,000 as part of its program of assistance to hospitals without tax support. The building was sold after 1978 and now is used for offices (figure 5). Assets of Babies Hospital, Inc. are managed as a charitable foundation supporting health care for children.

Dr. Sidbury was Medical Director of the hospital from its beginning until his death in January 1967. Early in his practice he had established milk stations in Wilmington to prevent summer diarrhea. He recommended early operation for congenital hypertrophic pyloric stenosis.[3] With the participation of surgeons Thomas Green, James Robertson, and Joseph Hooper, Donald Koonce, and others more than 100 patients were operated upon. He made the diagnosis, corrected dehydration, and often administered anesthesia. In 1923 he reported using the umbilical vein for transfusion of the newborn[5] and later used this route for exchange transfusion in neonatal jaundice. Dr. Sidbury's reputation resulted in an inordinately large referral area. Although Babies Hospital served eastern North and South Carolina primarily it was not unusual for patients to come from other east coast states.

The first president of Babies Hospital, Inc. was Mr. Thomas H. Wright. He was followed by Mr. Thomas H. Wright, Jr., Mr. Walker Taylor, III, and Lt. Gen. (ret) George S. Boylan.

An account of Babies Hospital would be incomplete without mentioning Miss Alice K. Schulken who was the Superintendent of the Hospital and of Nurses for 27 years. The title does not include that she also planned the meals, did the purchasing, supervised housekeeping and grounds including an outstanding rose garden, often working 18 hour days 7 days a week.



Figure 5. *Babies Hospital Building, 1983.*

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4. Green TM, Sidbury JB: Hypertrophic stenosis of the pylorus in infants. Surg Gynec & Obst 159-164, Feb. 1919.
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Acknowledgment

The author expresses thanks to Miss Willa Dickey for providing much of the material on which this account is based, to Mr. Ashley Gale, Jr., of the Duke Endowment for statistical information, to Lt. Gen. George Boylan for additional information, and to Mr. Geoffrey Honaker for photography.

ADDENDUM

Life with Father

James B. Sidbury, M.D.

IT was a rather serious business. He was dedicated totally to pediatrics but it was quite clear to his children that he took his responsibilities as a father quite seriously. He was remarkably flexible in his approach to rearing but was inflexible in his belief in the importance of education.

His one avocation was quail hunting. He was good at it. Even when he hunted a full day it didn't seem to tire him. I was often invited along. I did tire and I was a wretched shot. I suspect the only quail I ever "shot" were those he shot and gave me credit. The salutory aspect of the hunting trips insofar as I was concerned was the traveling to and from the hunt. These were some of the rare occasions we would have together. The conversation usually drifted to medicine or teachers he had known and how they had influenced his life.

As an adult I learned he was really quite a different person from the stoic and spartan individual I had known as a child.

He really had quite a good sense of humor; dry, a bit droll, but a good sense of humor. My favorite story is one told to me in part by Mr. Steve Harwood in the comptroller's office at Duke University.

My father had been a virtual walking medical text book the last two years of his life; having one condition after another. Enough to destroy the sense of humor of most men. He had a number of stays at the Duke Medical Center.

On the occasion of one of his admissions I contacted Dr. Barnes Woodhall, who was then Dean or Provost, and told him he should approach my father about giving money to establish a chair in Pediatrics. I told him that my father would not take it seriously if it came from me. Dr. Woodhall was successful. A day was decided when the transaction was to take place. My father with a paper bag, Dr. Woodhall and Dr. Anlyan met and went to Mr. Harwood's office to deliver the securities which would establish the Pediatric Professorship. They arrived at Mr. Harwood's office; the paper bag was proffered. Mr. Harwood, replete with green shade, counted the securities. He looked up and said, "Dr. Sidbury, that's not enough." Whereupon my father reached into his right inside pocket and introduced additional securities. Dr. Woodhall and Dr. Anlyan were terribly embarrassed. Mr. Harwood counted the additional securities and said, "Dr. Sidbury, that's still not enough." My father calmly pulled additional securities from his left inside pocket. Conversation at this point was indeed a bit awkward. Mr. Harwood counted and noted the total was sufficient. Few would ever have suspected my father was capable of such a practical joke, especially not Dr. Woodhall or Dr. Anlyan. It also illustrates what the poor Deans and Provosts have to handle in the pursuit of money!

From the National Institutes of Health, Bethesda, MD 20205.

ADDENDUM II

Forty-five Years with Dr. Sidbury

Willa M. Dickey

ON June 6, 1933 I arrived by train in Wilmington to spend three months working with Dr. Sidbury at his offices in town and at the Babies Hospital. I rode the street car to the front yard of the hospital on Wrightsville Sound just across the Inland Waterway from the beach. For a number of years that was the main transportation for the hospital staff. My three months extended until the hospital closed 45 years later. To me, Babies Hospital and Dr. Sidbury were synonymous.

Each fall he spent several weeks at one of the leading pediatric institutions keeping up with advancing technology. One of the first oxygen tents in North Carolina was made locally following instructions brought back from his "vacation." There were no oxygen gauges at that time.

Most of the pediatric problems requiring unusually intensive study were referred to Boston, New York, Philadelphia, Baltimore, St. Louis, or Richmond. When Duke Hospital began operations Babies Hospital was still the state's pediatric center. Partly to remedy this, Dr. Sidbury was appointed to the Board of Directors of Duke and served in that capacity for many years. He referred more and more patients there each year.

He gave the first doses of tetanus toxoid in North Carolina. Soon after receiving his booster dose, a doctor's child suffered a depressed compound skull fracture. The drug was so new that neither the surgeon nor Dr. Sidbury was willing to trust the toxoid and antitoxin was given.

The first dose of streptomycin given in North Carolina was to a little patient from the Lake Waccamaw area.

At one of the meetings of the North Carolina Pediatric Society held at Babies Hospital, Dr. W. C. Davison and Dr. Sidbury presented the question of mandatory administration of DPT. Dr. Davison was unanimously asked to follow up on this and a state law was soon enacted.

Resident physicians from Yale, New York, St. Louis Children's Hospital, Philadelphia and Johns Hopkins were sent on a rotating basis so that they might become more accustomed to dealing with private practice and with mothers staying with their sick children. This assured Babies Hospital of an excellent resident at all times.

For many years, Dr. Sidbury was the only member of the American Pediatric Society not associated with a large hospital or teaching institution.

Many poliomyelitis and diphtheria patients owe their lives to treatment received at Babies Hospital, and I owe much of the satisfaction of my life to the same institution, its staff members, its patients, but particularly to its founder and director, Dr. J. Buren Sidbury (Figure 6).

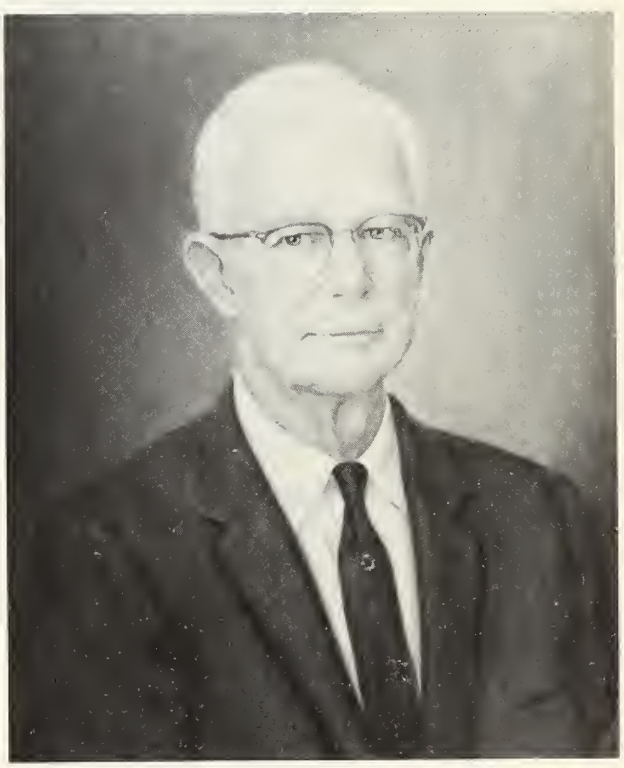


Figure 6. *Photograph of a portrait of Dr. Sidbury.*

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Bulletin Board

Announcement of a Trial in Process

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To refer a patient or to obtain further information, call or write David N. Danforth, Jr., M.D., Admitting Officer, Surgery Branch, National Cancer Institute, Building 10, Room 10N119, Bethesda, MD 20205. 301/496-1533.

North Carolina Names in the News

The North Carolina Division of the American Cancer Society held its annual meeting on October 29-30 and elected new officers. New President is Walter B. Love, Jr. of Monroe; Chairman of the Board is **Avery McMurry, M.D.,** of Shelby. Other officers elected were **Charles L. Spurr, M.D.,** of Winston-Salem, President-Elect; Ruth Dublin of Smithfield, First Vice President; **Lawrence K. Boggs, M.D.,** of Charlotte, Second Vice President; Johnsie Setzer of Claremont, Secretary; Wesley Allen, M.D., of Fayetteville, Assistant Secretary; J. T. Lindley of Raleigh, Treasurer; H. John Hatcher of Raleigh, Assistant Treasurer; and Roger O'Quinn of Raleigh, Executive Vice President.

The Eye-Bank Association of America, Inc. awarded **Lawrence B. Holt, M.D.,** of Winston-Salem the R. Townly Paton Award for distinguished service rendered the world in the development of the eye-bank movement. Dr. Holt founded the North Carolina Eye and Human Tissue Bank and helped found the Eye-Bank Association of America, of which he was the first ophthalmologist-president.

The North Carolina Surgical Association held its fall meeting at The Greenbrier in White Sulphur Springs, West Virginia, September 29-October 2. Their officers for this year are **Dr. Fred Taylor,** President; **Dr. James Davis,** Vice-President; **Dr. Henry Wilson,** Secretary-Treasurer.

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

January 1984

"Advanced Seminar for Certification in Administrative Psychiatry"
Place: Chapel Hill
Credit: 32 hours
Info: Malinda Marsh, Department of Community Psychiatry, UNC School of Medicine, Wing D, 208H, Chapel Hill 27514. 919/966-5277

February 3-4

"Live from Duke — Pediatrics 1984"
Place: Durham
Credit: 11.5 hours, Category I AMA; PREP
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 6

"Records and Other Necessities"
Place: New Bern
Info: Wayne Parker, Medical Mutual Insurance Company, Box 27444, Raleigh 27611. 919/828-9334

February 17-18

"Clinical Teaching"
Place: Chapel Hill
Fee: $275.00
Credit: 12
Info: Ms. Ruth De Blíek, ORDEHP, UNC School of Medicine, 322 MacNider Bldg. 202H, Chapel Hill 27514. 919/966-3641

February 19-22

"Beyond Advanced Clinical Teaching Skills"
Place: Rougemont
Credit: 20 hours Category I AMA
Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

February 20-22

"Selected Topics for the Practicing Clinician"
Place: Durham
Credit: 24 hours Category I AMA
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 24-26

"NCSIM/NC-ACP Joint Meeting"
Place: Greenville
Info: Kathy Adams, North Carolina Medical Society, Box 27167, Raleigh 27611. 919/833-3836

March 1-3
"2nd Annual Diving Accident Symposium"
Place: Durham
Credit: AMA, AAFP, ACEP
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 6
"Duke Tuesday"
Place: Durham
Credit: 5 hours Category 1 AMA
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

March 7-10
"Internal Medicine: 1984"
Place: Chapel Hill
Credit: 25 hours AMA Category I
Fee: $250.00
Info: William B. Wood, M.D., 231 MacNider Bldg 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

March 15-16
"Eighth Annual Cancer Research Symposium"
Place: Chapel Hill
Credit: 11 hours AMA Category I
Info: Mrs. Mimi Minkoff, Cancer Research Center, UNC School of Medicine, Chapel Hill 27514. 919/966-3036

March 18-21
"Improving Residency Rotations: Curriculum Planning and Negotiation"
Place: Rougemont
Credit: 20 hours Catetory I AMA
Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

March 28-31
"Clinical Epidemiology"
Place: Chapel Hill
Credit: 24 hours
Info: Ruth De Bliek, 322 MacNider Bldg. 202H, UNC School of Medicine, Chapel Hill 27541. 919/966-3641

April 7
"13th Annual New Bern Symposium: Infectious Disease"
Place: New Bern
Info: William B. Hunt, Jr., M.D., Box 2157, New Bern. 919/633-8607

April 8-11
"Administrative Skills: Faculty as Managers"
Place: Rougemont
Credit: 20 Hours Category 1 AMA
Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

April 10
"37th Annual Medical Symposium: Pulmonary Medicine"
Place: Greensboro
Info: L. S. Slotnick, M.D., 1018 North Elm Street, Greensboro 27401 919/275-7238

April 11-14
"3rd Annual Spring OB/GYN Symposium"
Place: Durham
Credit: AMA, ACOG
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

April 12
"North Carolina Neuro-ophthalmology Review"
Place: Chapel Hill
Credit: 2.5 hours Category I AMA
Info: Baird S. Grimson, M.D., UNC School of Medicine, Chapel Hill 27514.

April 20-21
"Carolina Ocutome Workshop"
Place: Chapel Hill
Credit: 13 hours Category I AMA
Info: David E. Eifrig, M.D., UNC School of Medicine, Chapel Hill 27514.

OUT OF STATE

February 5-11
"Winter Conference in Internal Medicine"
Place: Snowshoe, VA
Credit: 20 hours Category 1 AMA
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 12-17
"Postgraduate Course in Diagnostic Imaging"
Place: Cancun, Mexico
Fee: $475
Credit: 25 hours Category I AMA
Info: Donald R. Kirks, M.D., Box 3834, Duke University Medical Center, Durham 27710. 919/681-2711, ext. 286 or 287

February 20-22
"Gold Coast Seminar: Surgery"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 22-25
"Medical Computing"
Place: Key Biscayne, FL
Credit: AMA, AAFP
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 4-10
"Sports Medicine"
Place: Snowshoe, WVA
Credit: 20 hours AMA Category 1
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 5-7
"Gold Coast Seminar: Pediatrics"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 8-11
"New Horizons for Psychosomatic Medicine"
Place: Hilton Head, SC
Credit: 20 hours Category I AMA
Info: Joan K. Erpf. 316/379-0191

April 9-11
"Gold Coast Seminar: OB/GYN"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

In Memoriam

Edgar Vernon Benbow

Edgar Vernon Benbow, M.D., died at his home in Winston-Salem July 18, 1983 at the age of 84. He was a graduate of East Bend High School, the University of North Carolina, its two year Medical School and Jefferson Medical College. He interned and had residency training in Brooklyn Hospital and did post graduate work at the University of Pennsylvania and the University of Vienna. He served as Private in World War I and Major in World War II.

He was a diplomate of the American Board of Surgery and a qualified fellow of the International College of Surgeons. He did distinguished general surgical practice in Winston-Salem for thirty-one years and retired in 1958. He was twice President of the Staff at Baptist Hospital and twice Chief of Staff at City Memorial Hospital.

He was a member of the Oasis Temple of the Mystic Shrine and a member of Centenary Methodist Church. He was successful in business and gave generously to the Yadkin County Public Library, Guilford College, and the University of North Carolina.

He is survived by his wife Sue Satterwhite Benbow, children Carolyn, Vernon, and William and five grandchildren.

John H. Rosser, M.D.

John H. Rosser, M.D. died on June 23, 1983. Dr. Rosser attended Wheaton College in Wheaton, Illinois, received his medical degree from the University of Maryland in 1947, and then served a surgical residency at Emergency Hospital, Washington, D.C., Women's Hospital in Baltimore, Maryland, and the University Hospital at the University of Maryland. He served in the United States Air Force from 1950 to 1953.

He established his practice in Statesville in 1955, where he practiced until his death.

He served the medical community as a member of the American Medical Association, the North Carolina Medical Society, and the Iredell County Medical Society, and was a Fellow of American College of Surgeons. He served his community in various capacities, including being a Deacon of the First Baptist Church and chairman of that body for many years. He is survived by his widow, Pearl; his daughters, Deborah Kesler and Susan Wittig; and his sons, David and Dr. Stephen.

Charles Baynes Wilkerson, Jr., M.D.

Dr. Charles Wilkerson, beloved Raleigh internist, died on April 29, 1983, at the age of 64.

He was a graduate of the University of North Carolina and the Medical College of Virginia. He served an internship and residency at Rex Hospital before entering the U.S. Army immediately after World War II. On his return, he completed his training in Internal Medicine in the V.A. Hospital system, and then came back to Raleigh to join his sister, Annie Louise, in practice.

As evidence of his interest in high standards of education and practice, he served for six years as a member of the North Carolina Board of Medical Examiners, including one year as Chairman. He was also a past president of the Rex Hospital Staff and of the Raleigh Academy of Medicine.

Dr. Wilkerson was also interested in driver safety. He was the original and only Chairman of the State's Driver Medical Review Board set up in 1967 legislation to evaluate the competence of drivers with health problems. His colleagues in practice, in the Division of Health Services, in the Department of Motor Vehicles, and in the Attorney General's Office were quick to praise his objectivity, thoroughness and fairness.

He was a life-long member of the Edenton Street United Methodist Church. He had served as President of its governing body and was the current President of its Endowment Fund.

Dr. Wilkerson is survived by his wife Lib, his daughter Beth, sisters Annie Louise and Margaret Flint, and brother Louis.

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Letters to the Editor

An Appliance for the Blind

To the Editor:

I was pleased to see the October issue of the *North Carolina Medical Journal* with its patient section devoted to information to help patients with visual problems that cannot be corrected. My sister has recently become blind. She had no way of determining the time of day; on awakening from sleep she didn't know whether it was morning or night. We bought an alarm clock from Radio Shack that tells the time audibly every hour on the hour or whenever the button on its top is depressed. It is available from most Radio Shack stores or through their catalog for $39.95. A suction cup attached to the bottom of the clock so that it won't be knocked off the table by a sleepy hand would be helpful.

Alice Cleland
Methodist Retirement Home
Durham 27705

The Ophthalmology Issue

Dear Doctor Hughes: (one of the Editor's bosses)

How kind of you to seek me out at the Homestead and comment so kindly on the *Virginia Medical Journal*. It was ever so generous of you.

On my return I made my way to your October issue with the ophthalmologic theme — an excellent issue, beautifully put together and presented. And what a good idea, to publish not only for your doctors but for their patients! Toward which worthy goal your "Features for Patients," pages 645-656, is simply splendid, with its lively drawings and helpful information. My compliments!

Ann Gray, Executive Editor
Virginia Medical Journal
4205 Dover Road
Richmond, VA

Oozing and Bruising

To the Editor:

I wish to compliment Dr. John Stuart and Virginia Burnette on their November scientific article. This discussion of von Willebrand disease and qualitative platelet defect was concise, clear and pertinent — just the ticket for practicing surgeons. Keep up the good work!

Randall D. Johnson, M.D.
16 McDowell Street
Asheville 28801

Long-term Results in Spastic Dysphonia

To the Editor:

In the June 1983 issue, an article entitled "Spastic Dysphonia Helped By Clipping Recurrent Laryngeal Nerve" by Drs. Patrick D. Kenan and John E. Riski was of considerable interest but I felt did not quite go far enough. Certainly the recurrent laryngeal nerve section for spastic dysphonia has gotten considerable publicity in the head and neck literature but may not have been well publicized in other fields. However at this time, there are reports now being published raising question as to the long-term results. Drs. Dedo and Izdebski reported that a majority of patients reported subjective improvement in their voices immediately, and four years postoperatively, 80% gave unqualified recommendation for the operation while 20% expressed some reservation about the surgical treatment of spastic dysphonia (*Laryngoscope* 93:9-16, 1983).

Drs. Aronson and DeSanto found that after three years only 36% of the patients had any improvement in voice as compared with preoperatively and a significant percentage of patients had a voice that was classified as worse than before surgery. They concluded that recurrent laryngeal nerve surgery for adductor spastic dysphonia has long-term limitations (*Laryngoscope* 93:1-8, 1983).

I have found it important in my practice to inform patients of these long-term consequences and results. I likewise feel it is important when we report to our colleagues that these results be given as well so as not to perhaps falsely raise the patient's hopes and expectations.

William B. Costenbader, M.D.
131 McDowell Street
Asheville 28801

Dr. Kenan replies:

Thank you for allowing me the opportunity to review the material sent you by my friend, Dr. William Costenbader. With his characteristic thoroughness, he has nicely crystallized some of the important long-term issues associated with the management of spastic dysphonia.

I am familiar with the papers he mentioned in his letter. Of the two, the paper by Dedo has, I believe, greater merit for several reasons. First, Dedo is the originator of the technique of the recurrent laryngeal nerve section for the treatment of carefully selected patients with spastic dysphonia. Second, he probably has the largest series of patients so treated of anyone in the world. And third, recognizing that this technique is not a cure-all for all such cases, he is very careful in his selection of patients for operative treatment. This paper does indeed mention alternate forms of treatment including removing the edge of the vocal folds by CO_2 laser or the use of teflon injection of the folds. His results of 80% improvement four years or more following nerve section represent to me a very positive endorsement of this technique. In comparison, the smaller series by Aronson and DeSanto registers a success rate of only 36%. Even this rate of success has a certain merit because it translates into one out of three successes in comparison with almost a 0% success rate for speech therapy or psychotherapy as the only treatment modality.

Dr. Costenbader is quite right in emphasizing the need to inform patients of long-term results. I would emphasize again the standard diagnostic test is a Xylocaine injection of the left recurrent laryngeal nerve with noting of the immediate effects thereof. Others have emphasized that even a good result using an anesthetic agent might well justify a repeat effort with a placebo injection of sterile saline in

order to separate the purely psychogenic problems from the truly neurogenic.

In summary, very careful patient selection remains the most important criterion in choosing patients for the recurrent laryngeal nerve section and each patient so selected must be informed that at best there are four out of five chances for long-term benefit.

Patrick D. Kenan, M.D.
Duke Hospital
Durham 27710

An Anlyan Story

To the Editor:

I attended the Duke University Medical School Alumni Reunion (Class of '48) recently and would like to congratulate Dr. William Anlyan on the honors he received during the Reunion. The Central Tower of the new hospital was named in his honor.

This recognition was just reward for the many things that Bill has accomplished for Duke University since he came to Duke after graduating from the Yale Medical School 33 years ago.

I would like to relate to you a story known only to a few surgeons which involved the destiny of Dr. Anlyan and to honor and enhance the integrity of another of Duke's famous and beloved surgical teachers, Dr. Deryl Hart, who was chairman of the Department of Surgery at that time.

In 1951 the Korean War erupted and five of the surgical house staff residents (Drs. Gordon Carver, Marcus Dillon, Robert Gowdy, Eugene Lindberg, and Glenn Young), who were two years ahead of Dr. Anlyan in the surgical training rotation, volunteered and went to the Armed Forces. Dr. Anlyan was rejected by the armed services because of his ankylosing spondylitis. Two years later those five who had been in service returned to complete their surgical residency at Duke, and Dr. Hart found himself with six men at the same level of training. A decision had to be made as to who was to be the first to go through the surgical residency and who would be last.

At that time Duke was graduating a surgical resident qualified in general, thoracic, and cardiovascular surgery every six months. Dr. Hart's dilemma was that if Dr. Anlyan followed the five men who were two years his senior in experience and training it meant two and a half years in the laboratory waiting to get back into the surgical service rotation. If Anlyan went first, each of the other five would be set back only six months.

Dr. Hart solved the problem by calling these five young surgeons into his office, explaining the situation to them, and left them to decide Anlyan's fate. His parting remark was, "You men volunteered for and put your lives on the line for your country. I appreciate this very much, and you must decide whether Anlyan goes through the program first or last."

It meant only a six-month delay for each of us or a two and a half year delay for Bill. We decided to let Dr. Anlyan go first through the residency ahead of us. I think we had a premonition that he might go back to Yale if he had to wait, and we didn't want to lose him. His contributions to Surgery and to Duke proved this to have been a good decision.

I don't know whether Dr. Hart revealed the intricacies of this decision to Dr. Anlyan. Perhaps Dr. Anlyan will respond to this letter.

Gordon M. Carver, M.D.
1202 Broad Street
Durham 27705

A Davison Story

To the Editor:

I think that the *Journal* can stand one more Davison letter.

In 1936 I had been dating a Miss Mary Carter who was an assistant head nurse on one of the Duke wards. She had recently been hired by Dr. Max Oates, surgeon, who had finished his residency in 1936 and was going back to his home town of Martinsburg, West Virginia where his father owned the hospital. They were planning to add pediatric beds and a nursery to the hospital. I was asked to come to Martinsburg and help with some of the details. I decided to go up to see Miss Carter and look over the hospital before deciding about working in Martinsburg. The problem was that I had no means for traveling to West Virginia.

Carl Rogers saw that I was really concerned about something and asked what was bothering me. (Carl Rogers was a black man called, by Dave, the assistant dean.) I told him that I wanted to make a trip to Martinsburg to see my girlfriend and look over the hospital there. He asked what I was worried about; I said that I didn't have any money to go up there but guessed I could borrow it from someone. Carl said, "Wait a few minutes, Dr. Gay," and returned in 10-15 minutes saying that Dr. Davison had agreed to let me borrow his car to go to West Virginia. Then Carl asked me if I had money to buy gas and I told him no, but I guessed I could borrow that from some of my friends. Carl said, "Wait a few minutes," and he came back in about 15 minutes and said that Dr. Davison was going to let him fill up the car with gas and lend me $10 to help me with the gas up and with other expenses. Gas was less expensive in 1936.

On the way up the radiator began leaking. I had not thought to check the radiator for water. It was therefore necessary for me to stop at different houses along the route and get water and my getting to Martinsburg was delayed. When I arrived I took the car to an automobile mechanic who said he could fix it for $10. Of course there was nothing else I could do but let him go ahead and fix it. In the meantime, Dr. Oates had been nice enough to say I could stay in one of the hospital rooms, therefore I did not need a hotel room.

Miss Carter and I, of course, had lots of fun looking over the hospital and city together although we did not have any money to spend. I returned safely back to Duke University Hospital having decided that I would accept Dr. Oates' invitation and go up for one to two years while they were finishing the wards.

A followup on this story has to do with 1948 when the Pediatric Society was having its annual meeting at Roaring Gap and Dr. Davison was the speaker. As secretary to the Society I was sitting next to Dave at Dinner. In the course of conversation, he asked me how I was getting along in Charlotte, and I said, "Pretty well. I am actually making a

little money." Dr. Davison took out a little black book which he kept notes in and turned to a certain page and looked at me and said, "Well, maybe you are doing well enough that you can pay back the $10 you borrowed from me back in 1936." Of course, I was a little embarrassed although I hadn't actually forgotten; I just didn't feel I was getting along that well. Anyway, when I got home I sent Dr. Davison a check for the $10 plus 6% interest for the years in between. Dr. Davison wrote me a note saying he appreciated the $10 but he had not intended to charge interest; however, since I had sent it he would give it to his favorite charity.

As a further followup, Miss Carter became Mrs. Gay June 29, 1937. We've been married 47 years.

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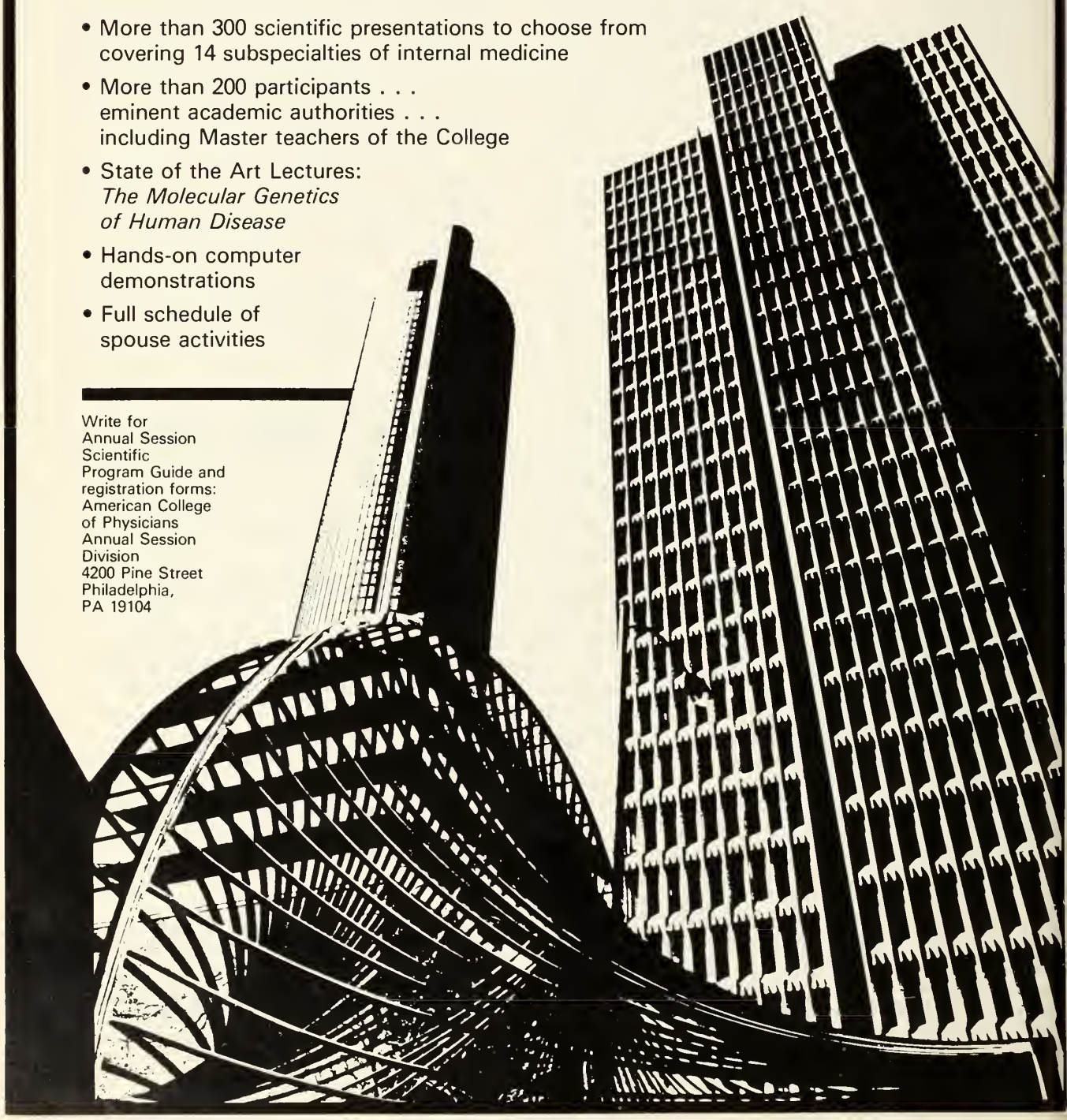
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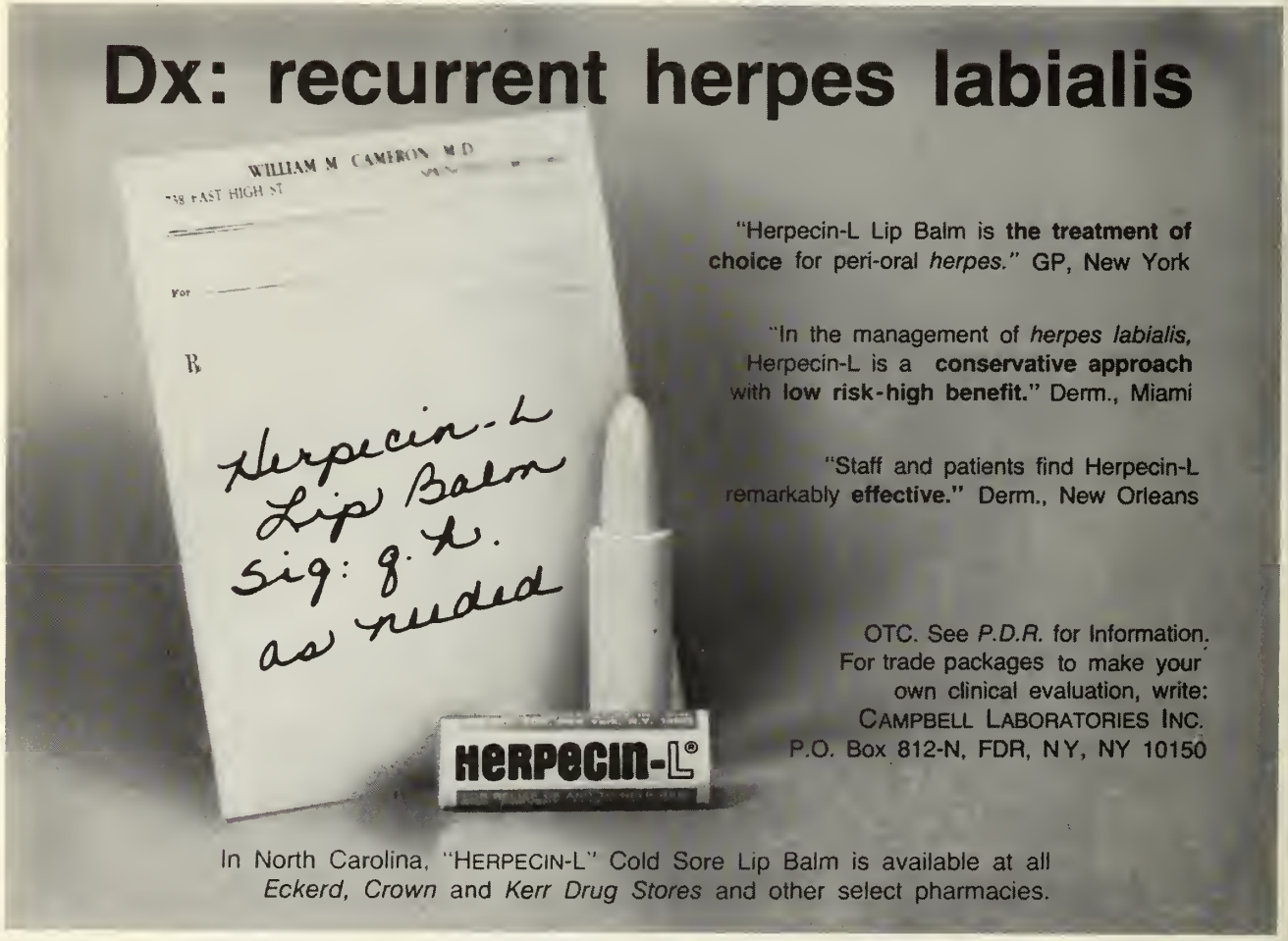
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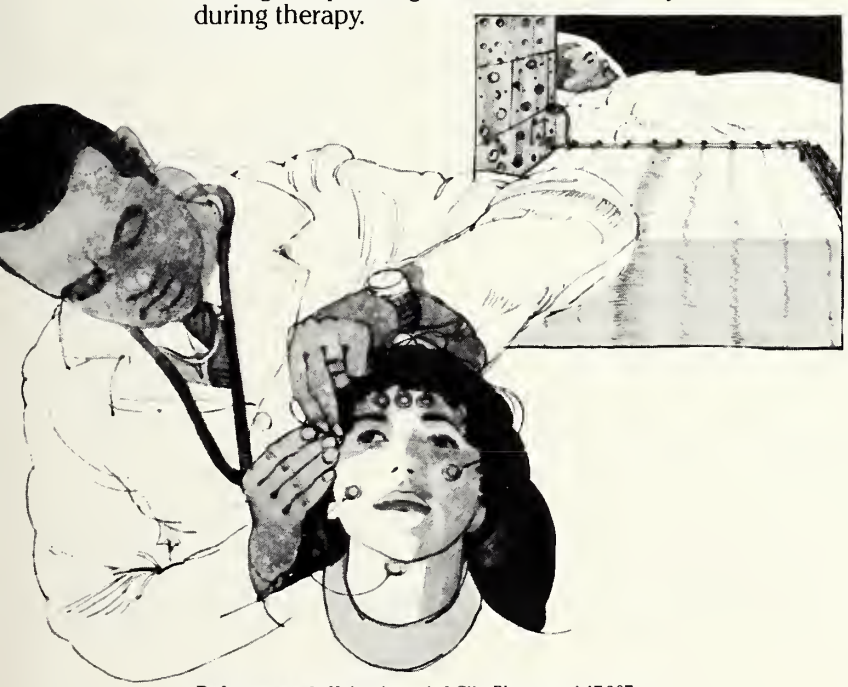
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References: **1.** Kales A *et al: J Clin Pharmacol 17*:207-213, Apr 1977 and data on file, Hoffmann-La Roche Inc., Nutley, NJ. **2.** Kales A: Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **3.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **4.** Kales A *et al: JAMA 241*:1692-1695, Apr 20, 1979. **5.** Kales A, Scharf MB, Kales JD: *Science 201*:1039-1041, Sep 15, 1978. **6.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **7.** Kales A, Kales JD: *Pharmacol Physicians 4*:1-6, Sep 1970. **8.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **9.** Dement WC *et al: Behav Med 5*:25-31, Oct 1978. **10.** Vogel GW: Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **11.** Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington, DC, May 3-7, 1971. **12.** Pollak CP, McGregor PA, Weitzman ED: The effects of flurazepam on daytime sleep after acute sleep-wake cycle reversal. Presented at the 15th annual meeting of the Association for Psychophysiological Study of Sleep, Edinburgh, Scotland, June 30-July 4, 1975. **13.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

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Income Maintenance in Retirement by Angela M. O'Rand

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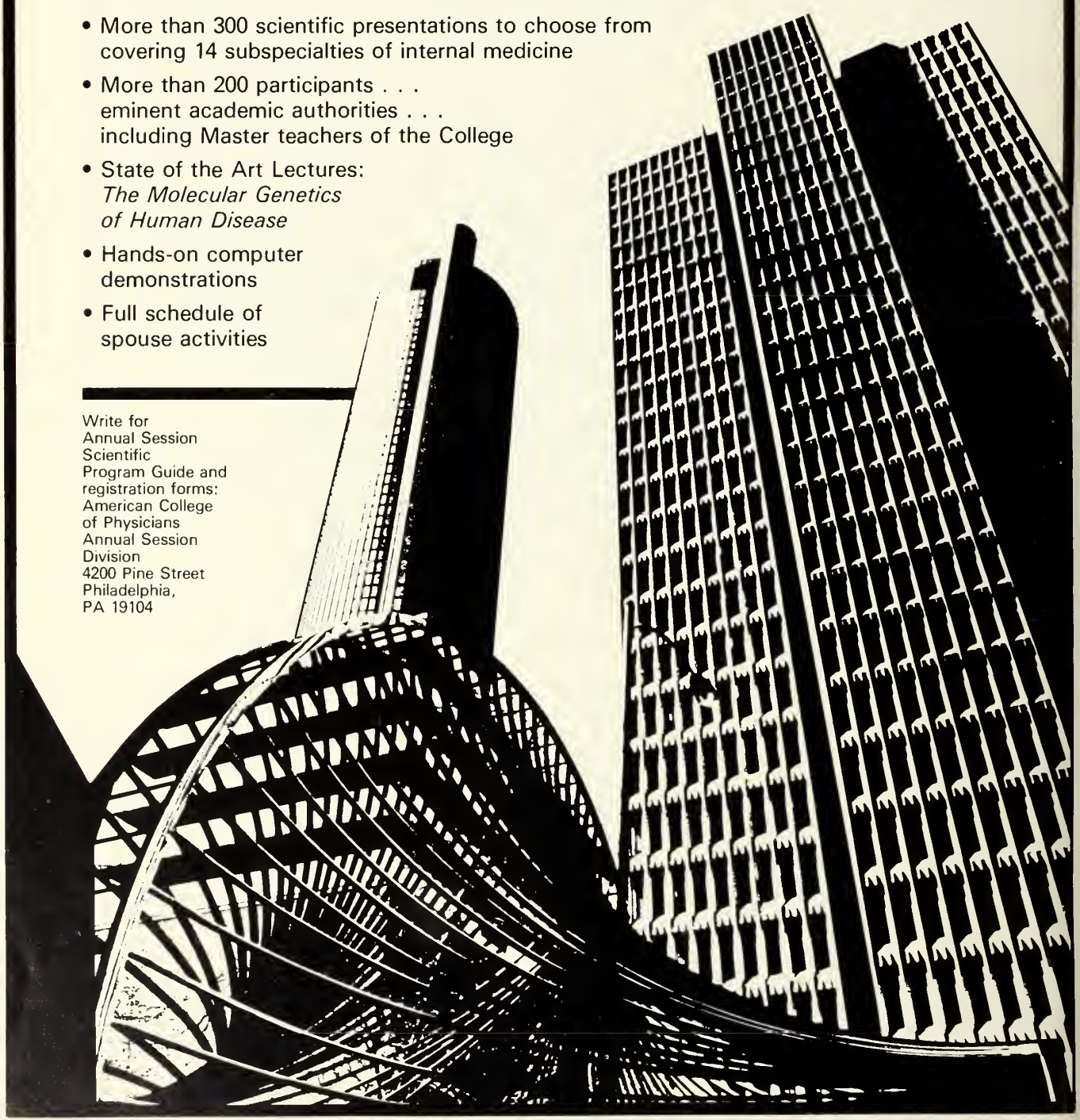
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Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms.

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae* (*Diplococcus pneumoniae*), *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor® (cefaclor, Lilly) is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGDT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.*

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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SCIENTIFIC ARTICLE

Alcoholism Treatment Today

Jack Donovan, William J. Reid, M.D., Sherwood W. Barefoot, M.D.

ALCOHOLISM is society's most urgent yet neglected problem. We know progressive drinking means death for the alcoholic, but few appreciate that uncontrolled alcoholism can also mean death for society as we know it.

Thirty years ago the American Medical Association recognized alcoholism as a disease and not a moral insufficiency. Despite that observation, alcoholism still ravages the world, constrained only by the limited, yet effective, treatment available today.

Alcoholism destroys not only its victim but many persons surrounding the victim. The physical, emotional, and spiritual essence of a person dissipates even as an aggressive denial blocks sociomedical assistance. Painful stress begets a dependency on sedative relief; the entire cellular system known as a person becomes disoriented, irresponsible, and corrupt. A delusional state results, often presenting as psychoneurotic, confounding and disrupting relationships, careers, lives, society in general — denying, defying diagnosis — much less treatment.

Is it any wonder that society saw fit for centuries to ignore these "immoral deviants" and did little to prevent their spiritual disintegration?

Today, as many as 15% of us suffer this dynamic biochemical corruption called alcoholism — adversely affecting, directly or indirectly, nearly half of the earth's population and productivity.

Historically, society has found itself in a double-bind that has effectively blunted attempts to stem the destruction of alcoholism. Sales of alcohol account for an influential share of the gross national product. Despite society's habitual tendency to avoid self-imposed penalty at the expense of the few "deviants," new and specific legislation has been inspired by the painful experience of alcoholism's untold victims. Especially in the area of drunk driving, focus is concentrating on those whose behavior is dysfunctional, destructive, and unacceptable. Literally millions of offenders will be seeking treatment to resolve or at least ameliorate their "court-defined" drinking problem. By virtue of their advisory capacity, physicians will be involved because a disease is on trial. Physicians must be prepared to know the disease and methods of treatment.

An industrial reality now, alcoholism treatment came into being only recently in the long history of alcoholic dysfunction. If enthusiasm in the field can be equated with treatment effectiveness, success has been outstanding.

Treatment facilities vary in the specifics of their physical plants and programs but they generally subscribe to the *disease concept* providing abstinence as prerequisite of a rigorous program for physical health, self-evaluation/reconciliation, and permanent remission through a reordering of spiritual values.

Briefly reviewed, treatment facilities (centers) share several basic characteristics.

General Setting. Whether skyscraper suite or rural cottage, facilities offer a certain bed capacity (30-60 average) usually portioned or segregated by sex, and sometimes as well for adolescent and geriatric, with 2 to 4 beds maintained for the acute care phase of early recovery. Some are physical extensions of medical or psychiatric hospitals, others free-standing; but in any case they are normally a medical setting adhering to requirements of the Joint Commission on Accreditation of Hospitals. Most often patients are monitored by nurses operating within the controlled environment. Primary effort is aimed at providing an unrestricted "community comfort" that enhances personal respect and self-discipline as a vital part of recovery. At least minimal housekeeping service is available at most facilities (more at some); however, many apply "participation" therapy involving the patient in service activity: cleaning, cooking, and such.

Recreation in posh treatment centers may include formal exercise, golf, swimming, and horseback riding. Equally successful facilities may provide only pool and/or cards. Patients seem to welcome the opportunity for visitation and meditation on the extensive grounds of suburban centers while others find enjoyment in occupational (arts/crafts) therapy. Appropriate audiovisuals are made available to the serious intellects. At the same time, special programs are provided for the exceptional patients.

Admission. Cooperation between the facility and the admitting physician is preferred, and imperative if treatment is to be effective. Patients treated for alcoholism in an Employee Assistance Program or by practicing physicians interested in alcoholism profit from the contact with doctors alert to the natural history of this disease and to family dynamics that may perpetuate the problem. Though some physicians need more experience in diagnosing, recognizing symptoms, and routinely requesting a drinking history, increasing numbers of doctors are accepting the reality of formal alcoholism treatment. Success rates of 75% plus which have been reported for persons treated in an Employee Assistant Program are creating more interest among the profession.

The goal of admission screening is to determine the patient's appropriateness for the available treatment regimen. Though most programs stipulate a minimum 3 to 4 weeks, all treatment is individualized and flexible to allow for extension or special attention as required in acute care patients who will revert to their own physician for followup. Thus the physician is a conduit through which most

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victims, alcoholic and/or family, find help and remission, and continues to provide a consistent reference point after treatment.

Medical. Acute alcoholism provides progressive physical deterioration in all body systems, presenting symptomatic patterns that challenge the eager diagnostician; alcoholism masquerades as heart disease, diabetes, chronic high blood pressure, polyneuropathy, gastritis, insomnia, and arthritis, among others. Many, if not most, of these symptoms miraculously vanish in short order during treatment as the body begins to shrug off the effects of the systemic toxicity.

Most patients receive tapering doses of a tranquilizing compound to relieve the trauma of withdrawal. Other appropriate medications indicated by the admission physical examination (and/or as directed by the referring physician) are dispensed by a medical team as they monitor the patient's progress, effectively providing a formal record of diagnosis, treatment, and progress as well as a discharge summary and prognosis. Repeatedly throughout therapy, the patient is reminded of the responsibility he must assume for his own psychological/physical health. With rare exception, treatment programs stress a life free of any mood-changing chemicals.

Therapy. Coincident with and complementing the medical/physical efforts, teams of trained, professional counselors — usually armed with insight born of extensive personal experience — provide education and role model support as they interact with and monitor the patient in the restorative process. Individual and group therapy is a dynamic part of most treatment regimens. As the abstinent patients become physically restored, they find a strength of purpose in the commonality of their grief. Hope is rekindled and self-esteem reborn; life without sedation and dishonesty appears possible, even preferable. They learn to laugh with each other and at themselves as they inventory the motivations, values, and actions that are to carry them into and through sobriety. *Fact:* stopping drinking is not enough.

Today's treatment appreciates the necessity and benefits of family involvement, providing a dynamic educational experience as basis for support, understanding, and change when treatment is complete and recovery begins. Family treatment is receiving expanding attention as some facilities commence formal inpatient family therapy.

Aftercare. Patients are counseled to appreciate alternatives for ancillary support (AA, Al-Anon, Alateen) or extended treatment. Personal contact is offered for the year following discharge. Hospital house organs, such as newsletters, alumni associations, and/or reunions are not uncommon.

Conclusions. Today's alcoholism treatment is professional and effective. It is part of a team effort that includes the intervening physician in a continuum of commitment to alleviate the major societal dysfunction and personal tragedy known as alcoholism.

A Note from the Editor:

I was skeptical of the success rate of 75%. I asked Dr. Jack Ewing, chairman of the North Carolina Medical Society Committee on Drug Abuse and Pharmacy for his opinion. He replied as follows:

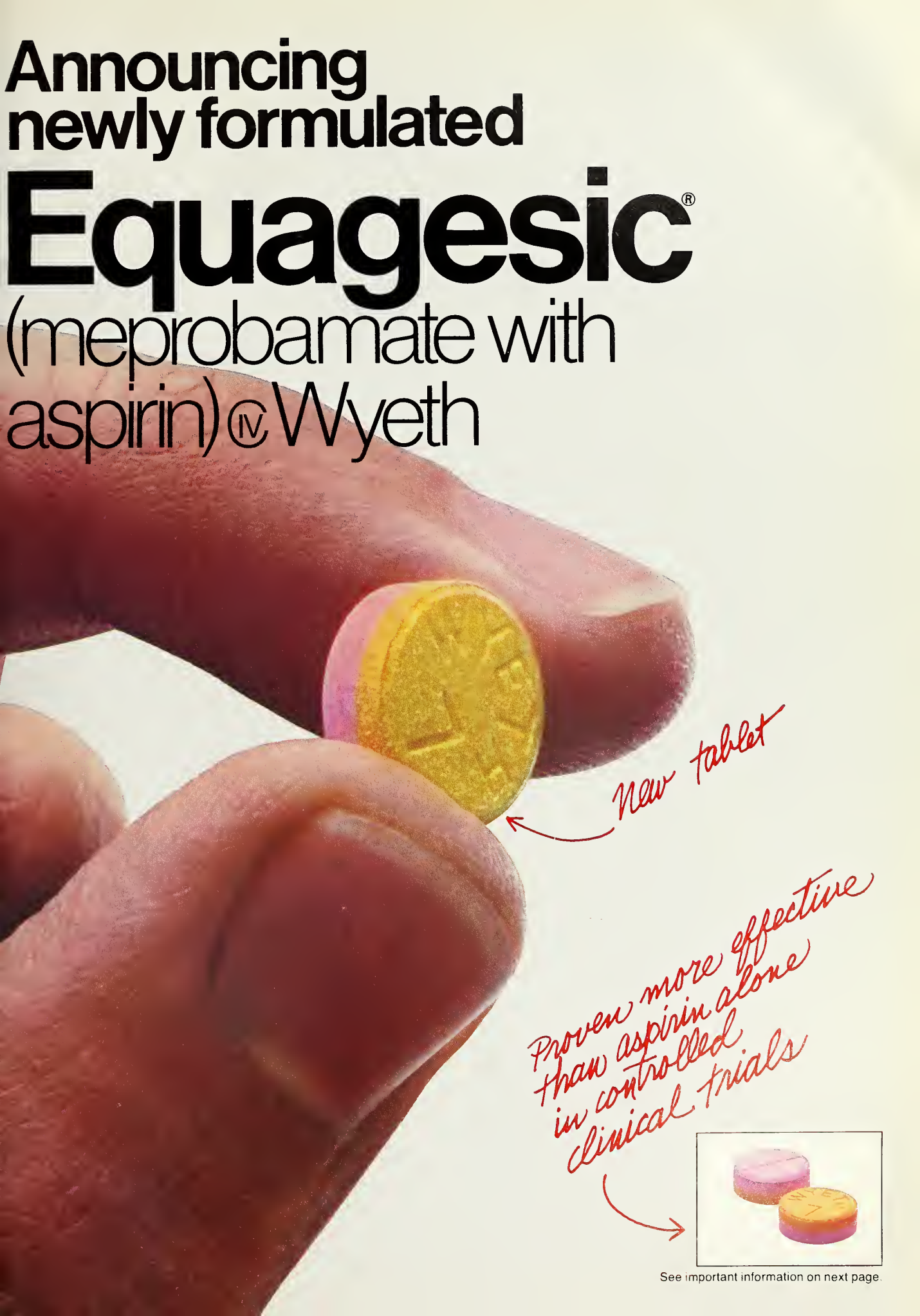
"The claim of 75% success rate has been documented by some industrial corporations that have employee assistance programs. Identified alcoholic employees who have been sent to treatment programs such as the one offered by Fellowship Hall do seem to achieve success rates in terms of continued abstinence for several years at least in the region of 75%. This is one of the great advantages of having a considerate employer who is, nevertheless, willing to provide coercion.

"The doctor in general practice who cares for patients not enrolled in a corporate employee assistance program will not have a 75% success rate."

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(BRIEF SUMMARY)

DESCRIPTION:
Each tablet contains 200 mg meprobamate and 325 mg aspirin

INDICATIONS:
Adjunct in short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease. Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone. Effectiveness in long-term use, i.e. over 4 months, has not been assessed by systematic clinical studies. Physicians should periodically reassess usefulness of drug for individual patients.

CONTRAINDICATIONS:
ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria, allergic or idiosyncratic reactions to meprobamate or related compounds, e.g. carisoprodol, mebutamate, or carbromal.

WARNINGS:
ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE: DRUG DEPENDENCE
Physical and psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually, greater than recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms, e.g. anxiety, anorexia, or insomnia, or withdrawal reactions, e.g., vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinosis, and, rarely, convulsive seizures. Such seizures are more likely in persons with CNS damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation, symptoms usually cease within next 12- to 48-hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e.g., driving or operating machinery.

ADDITIVE EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION:
An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug.

Meprobamate passes the placental barrier. It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS:
ASPIRIN: Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney, to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS:
ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS: Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity.

GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate/mebutamate and meprobamate/carbromal. Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC"): Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms.

DOSAGE AND ADMINISTRATION:
Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSAGE:
Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdosage produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole-blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal. The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported. Acute simple overdose (meprobamate alone): Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS:
0.5-2.0 mg percent represents usual blood-level range of meprobamate after therapeutic doses. The level may occasionally be as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdosage, such as stupor or light coma.

10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment. Some fatalities occur.

At levels greater than 20 mg percent, more fatalities than survivals can be expected.

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol): Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated. Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption.

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SCIENTIFIC ARTICLE

Strongyloidiasis at North Carolina Memorial Hospital

Richard A. Davidson

IN two previous articles I have described case series of patients with ascariasis and giardiasis. Both of these infections involve young, reasonably healthy individuals, even in series collected in a referral hospital population; both may cause discomfort (especially giardiasis), but rarely cause serious illness. *Strongyloides stercoralis* is a nematode which affects an older population and, if untreated, may cause fatalities.

Life Cycle and Symptomatology

Strongyloides stercoralis is unusual among human parasites in that it is not an obligate parasite; it has a free living life cycle, which enables it to reproduce and survive in the absence of humans. The organism prefers moist, sandy soil as is frequently found in the eastern half of North Carolina. One of its larval stages, the filariform larva, has the capability of penetrating human skin, and this is how the infection is obtained. The microscopic larvae penetrate the skin of the foot and ankle most frequently, and may cause a pruritic erythematous rash, especially in persons who have been previously infected. The larvae travel via the circulatory system to the lungs, where they mature in alveoli. During this portion of the life cycle, the patient may develop wheezing, coughing, a hemorrhagic pneumonia, or no symptoms at all; most patients will develop eosinophilia during this maturation phase.

Breaking out of the alveoli, the adolescent worms are coughed up and swallowed, and reside and mature in the duodenum or jejunum. Another unusual aspect of the life cycle is that the parasitic stage is parthenogenetic; male adult worms are not tissue parasites, and are passed in the stool. The female adults, 2 mm long, live in the crypts of the small intestine, where they lay eggs in the mucosa. These eggs hatch, and the rhabditiform larvae that emerge are passed in the stool. These larvae are the diagnostic stage that is usually seen in the parasitology laboratory. Symptoms found in chronic infection are usually mild, and include intermittent abdominal pain, bloating, and diarrhea.

Difficulties arise when the rhabditiform larva, which cannot penetrate tissue, metamorphoses within the body to the filariform larva, which readily penetrates the gut wall, carrying enteric bacteria with it; this causes polymicrobial sepsis and the so-called hyperinfection syndrome, which may have an 86% mortality.[1, 2] Filariform larvae may be found in the sputum, urine, or central nervous system in addition to the stool. The hyperinfection syndrome is clearly associated with conditions that cause defective cell-mediated immunity, such as corticosteroid usage, hematologic malignancies, protein-calorie malnutrition, and leprosy;[3] it represents a medical emergency and requires intensive and immediate therapy. Some authors recommend evaluating all patients who are to be immunosuppressed prior to their therapy; this may be especially worthwhile in patients who have undergone renal transplants, a number of whom have died from hyperinfection.[4-6]

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Diagnosis

The diagnosis is made by finding larval forms, usually the rhabditiform stage, in the stool. Three stool specimens will diagnose between 80 and 92% of infected patients. Unfortunately a percentage of patients will have larvae demonstrable in duodenal aspirates in spite of many negative stools; those patients in whom there is a strong clinical suspicion of strongyloidiasis but multiple stools are negative should undergo some evaluation of duodenal material. The Enterotest, an encapsulated string which is swallowed and then retrieved, is relatively simple to use, only mildly uncomfortable, and is as sensitive as three stool exams.[7] Other methods of obtaining duodenal material, such as endoscopy and small bowel biopsy, are equally effective. Approximately 95% of infected patients will have over 5% eosinophils on differential white blood cell count. No reliable serum tests for diagnostic purposes are yet available.

Treatment

Thiabendazole is definitively the drug of choice in this infection, in a dose of 25 mg/kg/day, two divided doses per day on two successive days. This course of treatment may be repeated in 7 days, especially in immunocompromised individuals; this regimen will successfully treat over 96% of infected persons.[8] Careful followup to ensure a parasitic cure is highly recommended.

Case History

FB, a 59-year-old man from Roanoke Rapids, was admitted to NCMH for evaluation of recent symptoms of cord compression. He had a fifteen-year history of seropositive rheumatoid arthritis and active cervical spine disease had led to progressive weakness and loss of function in his lower extremities. He had been treated with prednisone, 10 mg every other day, for 4 years prior to admission. He denied any symptoms referable to the gastrointestinal tract, except for occasional indigestion after eating spicy foods. He specifically denied abdominal pain, bloating, nausea,

or vomiting. He underwent decompressive surgery by the neurosurgery service and was transferred to the rehabilitation service for the remainder of his admission. He was begun on penicillamine, and at that time was noted to have 7% eosinophils on differential white blood cell count. This was ascribed to his penicillamine, but it persisted after the drug was discontinued. Two stool examinations were negative, but an Enterotest revealed the presence of rhabditiform larvae of *Strongyloides stercoralis*. He was treated with two courses of thiabendazole, and at a followup visit 3 months later had no eosinophilia and stools were negative for ova or parasites.

Case Series

The records of all patients with proven strongyloidiasis at the North Carolina Memorial Hospital for the ten-year time period between 1971 and 1981 were reviewed. Forty-five patients were diagnosed; only forty charts were available for review. The forty patients had a mean age of 47.9 years; 82% were male and 67% were white. The mean eosinophil count was 15.3%; 37 of the 40 (92%) had greater than 5% eosinophils. Twelve of the patients were recent immigrants to the United States from Viet Nam, Cambodia, Laos, Africa, Haiti, and Puerto Rico. Sixty percent of the patients had gastrointestinal complaints: 30% had diarrhea, 22% abdominal pain, and 10% bloating. Thirty percent had evidence of a skin rash. Fifty-five percent had stools sent to the lab because of eosinophilia alone, 17.5% because of gastrointestinal symptoms, 15% because of both, and 12.5% for other reasons; thus, 70% of the patients could have been diagnosed only on the basis of eosinophilia. Coexisting diseases found in the forty patients are shown in table 1.

Table 1

Major Coexisting Diseases in Forty Patients With Strongyloidiasis

Peptic ulcer disease (12)
Multiple parasites (8)
Hematologic malignancy (5; 2 Hodgkins, 2 CLL, 1 ALL)
Non-hematologic malignancy (5; adrenal, hepatoma, breast, prostate, lung)
Severe coronary heart disease (3)
Rheumatoid arthritis (2)
Tuberculosis, histoplasmosis, disseminated granulomatous disease, hemophilia, chronic renal failure, ITP, and bronchiectasis each occurred once.

While no patients had documented hyperinfection syndrome, one ten-year-old child with acute lymphocytic leukemia died outside the hospital of sepsis at a time when his leukemia was in remission. He was taking prednisone, and had been diagnosed as having strongyloidiasis 3 months earlier. He was never treated for the infection. A postmortem examination was not done.

A control population was collected and compared with these cases. The results, which will be published elsewhere,[9] demonstrated statistically significant associations with the white race, male sex, corticosteroid usage, hematologic malignancy, and prior gastric surgery.

This case series is similar to others in the literature,[10, 11] and suggests that the average patient with strongyloidiasis is a white male, approximately 50 years of age, with an average eosinophil count of around 15%. Two-thirds have gastrointestinal complaints, usually intermittent in nature, including diarrhea, abdominal pain, bloating, nausea, and vomiting. Over half have serious underlying chronic illness. Patients with these characteristics should be evaluated for the possibility of strongyloidiasis, including duodenal evaluation when stools are negative; those patients who are immunocompromised should be vigorously investigated, as they are at great risk if untreated infection is present.

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SCIENTIFIC ARTICLE

Management of Nose Bleed

Patrick D. Kenan, M.D.

FEW of us go through life without experiencing minor nose bleed from time to time. For some, this can be a serious and even life-threatening event, particularly when associated with blood dyscrasias, severe hypertension, liver disease, and cancer. Fortunately, most problems of nose bleed are more of a nuisance than a threat and lend themselves to relatively simple principles of home or office management.

The commoner forms of nose bleed are related to venous bleeding from the anterior septum which can be controlled by external compression of the alar rims, followed by application of a cotton pack saturated with any topical vasoconstrictor and placed within one or both nasal vestibules. A bilateral anterior pack sandwiches the septum and usually results in more effective tamponade of the bleeding site than a unilaterally applied pack. This is a technique that patients prone to frequent recurrent nose bleed can be trained to do on their own whenever the need arises. All that is required is to have small cotton balls and a bottle of vasoconstrictor nose drops available and control can be achieved almost immediately. The packs can usually be removed within an hour or so.

When confronted in an office setting with the typical anterior nose bleed, the physician should apply some form of tamponade first, and consider some form of cauterization if the bleeding site can be accurately identified. Silver nitrate or even electrocoagulation is useful for this purpose, provided some form of topical or local anesthetic is applied first. In effect, this form of "spot welding" can achieve immediate and often lasting control, though it may be necessary to recauterize in ten to fourteen days before complete control and healing are achieved. This is a technique apropos to small children as well as the elderly, both groups being at high risk for nose bleed.

Oftentimes the cause of bleeding relates to dryness and cracking of the nasal mucosa, either from the natural atrophy that accompanies aging or from exposure to dry heat. These cracks or fissures often occur directly over a point of cartilaginous or bony deflection where the mucosa is stretched or easily traumatized. With such findings present in association with repeated bleeding tendencies, septal surgery to relieve the points of deflection may be curative.

More severe forms of bleeding may justify the application of nasal packs for several days at a time. One of the more comfortable anterior packs is made from folded or rolled Telfa, coated with an antibiotic ointment such as Bacitracin. This method of packing is far easier than applying long strips, and is especially appropriate in a clinical setting of limited equipment or illumination. A relatively inexperienced provider can apply a folded piece of Telfa as a tamponade, whereas it takes experience and equipment to apply strips of packing material effectively.

It should be emphasized that as a general rule, bilateral packing is more effective and indeed more comfortable to the patient than unilateral packing, as the former maintains equal and opposite pressure against the septum, sandwiching it between packs, whereas the latter is often inclined to cause an uncomfortable displacement of the cartilaginous septum to the opposite side.

More severe forms of epistaxis are usually associated with posterior or nasopharyngeal bleeding from branches of the sphenopalatine artery. This type of bleeding is not likely to respond to anterior packs unless they are vigorously applied against the nasopharyngeal mucosa. A posterior pack is usually indicated in this situation. The classical posterior pack is a complicated arrangement of strings tied around a rolled sponge. It is placed into the nasopharynx in a retrograde manner by first introducing a small catheter through the nostril and out the mouth, tying a retraction string onto the oral end of the catheter, and then retracting the catheter, thus pulling the pack into the nasopharynx. There is usually a drawstring left in place in the pharynx, or out the mouth and taped to the cheek. The drawstring extracts the pack at the appropriate time two or three days after its application. The posterior pack is usually secured in place by tying the nasal string over a rolled sponge at the nostril, after first applying a conventional anterior pack once the posterior pack is in place.

Placement of classical posterior packs is unpleasant to the patient and usually necessitates prior application of topical vasoconstrictors and anesthesia to the nose and throat. The packs are quite uncomfortable during the time they are in place, and usually justify the administration of sedatives or narcotic containing analgesics. Worse yet, upon removal of large bulky packs, rebleeding often occurs, necessitating repacking, which only adds to the existing misery.

A simpler and less traumatic form of posterior packing, though not always so effective, is the use of nasal or nasopharyngeal balloons. The simplest is a Foley catheter with a 15 cc inflated balloon which is inflated with air or saline. The catheter is inserted into the nasopharynx, anterograde through the nostril, the balloon is inflated, and then the catheter is pulled gently against the posterior choana and taped in place at the cheek. The size of the Foley catheter usually precludes the simultaneous use of anterior packing.

Other commercially available balloon catheters are specifically made for posterior nasal tamponade, and some are

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embellished with an additional anterior balloon which both serves as an anterior pack and secures the apparatus at the nostril. Unfortunately, these balloons have a high failure rate with rupture of the balloon being the most common fault.

Adjunctive measures in the office or home management of nose bleed include use of cold substances for their vasoconstrictor effects. External ice packs, ice chips p.o., ice water gargles are all useful measures. Conversely, ingestion of excessively hot food or drink with its attendant vasodilator effects should be discouraged. Head elevation to reduce venous pressure in nasal membranes is naturally desirable. Avoidance of heavy exertion or straining at stool secondary to constipation are to be avoided.

On removal of packs, vigorous nose blowing is to be avoided but good humidity in the inspired air, good nasal hygiene through normal saline douching, and removal of crusts or clots by the rhinologist are useful management techniques.

Salicylates and anticoagulants are counterproductive to controlling nose bleed and should be avoided, interrupted, or at least reduced in the acute management of nose bleed or in the post packing phase. Vitamin K administration may be indicated as well as the giving of fresh whole blood or plasma.

Certain severe forms of epistaxis simply will not respond to conventional packing and may require surgical ligation of the primary blood supply to the nose. This may be accomplished by anterior and posterior ethmoid artery ligation through a medial superior orbital approach, or through transantral ligation of the internal maxillary arteries which supply the sphenopalatine vessels. There is probably no role for external carotid artery ligation, though this was a popular approach in the management of severe epistaxis twenty or more years ago. There is an important place for embolization of the internal maxillary artery which of course requires vascular radiology resources with selective catheterization of the internal maxillary artery via the external carotid artery. Surgical and embolization methods are best accomplished in the setting of a hospital or medical center, often with input from the internist or hematologist in the management of severe hypertension, coagulopathy, liver failure, or blood dyscrasia.

Preventive measures in the patient prone to nose bleed include careful regulation and management of underlying causes such as hypertension, alcoholism, etc., avoidance of nasal trauma associated with overly forceful nose blowing, nose picking, etc., and the maintenance of good hydration of the nasal membranes and good humidity in the inspired air. Therefore, a good oral fluid intake, use of bedside vaporizers or room humidifiers, saline nasal douching, and topical application of water-soluble lubricants such as Vaseline, can be useful prophylactic measures in the prevention of nose bleed.

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SCIENTIFIC ARTICLE

Breast Reconstruction Following Mastectomy

G. Georgiade, N. Georgiade, R. Riefkohl, D. Serafin and W. Barwick

AN evaluation of approximately six hundred patients who have undergone breast reconstruction at the Duke University Medical Center reveals a number of interesting findings.

Reconstruction of the breast following mastectomy has become an accepted procedure and is being demanded by more and more patients as they become aware of the option of reconstruction. In the more than 600 patients whom we have reconstructed there has been no demonstrable evidence of any effect on the course of the initial disease. The patients are generally very well satisfied with the results and delighted with the fact that their ability to wear all types of clothing and to participate in active sports has been enhanced because they no longer have to wear an external mobile prosthesis. Psychologically many have expressed the opinion that they feel "whole" once again, which provides them with an emotional uplift.

In approximately 75% of patients who have had a mastectomy, the breast mound can be reconstructed by the simpler technique of placing a Silastic implant in the subpectoral subserratus muscle position in order to create a breast mound. This procedure usually necessitates a short one or two day hospitalization, and on occasion is carried out in our outpatient Surgicenter. Over 125 selected patients in our series elected to have the first stage of their reconstruction carried out on an "immediate" basis at the time the ablative surgery was performed. Utilizing this technique saves the patient an operative procedure with no compromise in the original ablative surgery. Approximately four to six months later the final matching of the breast mounds can often be accomplished if there is not too marked a dissimilarity in the breast mounds and no additional surgery such as a subcutaneous mastectomy is performed on the opposite breast (figures 1-5).

In our initial series of patients who had breast reconstruction there were many patients who had undergone the Halstead radical mastectomy. Because of the difficulty in reconstructing the surgical defect created by removal of the pectoral muscle during the initial radical procedure, it was difficult to obtain an adequate aesthetic result. The evolution of the newer techniques involving transfer of musculocutaneous latissimus dorsi flaps (figure 6) and more recently rectus abdominus flaps (figures 7 and 8) to the chest area has allowed us to reconstruct the entire defect. Occasionally it has been necessary for us to reconstruct the chest defect utilizing a latissimus dorsi musculocutaneous flap from the unoperated side transferring this as a "free flap" using microsurgical techniques (figure 9).

The missing nipple-areola complex is constructed at the final stage. At the present time the areola is constructed

From the Division of Plastic, Maxillofacial & Reconstructive Surgery, Duke University School of Medicine, Durham 27710.

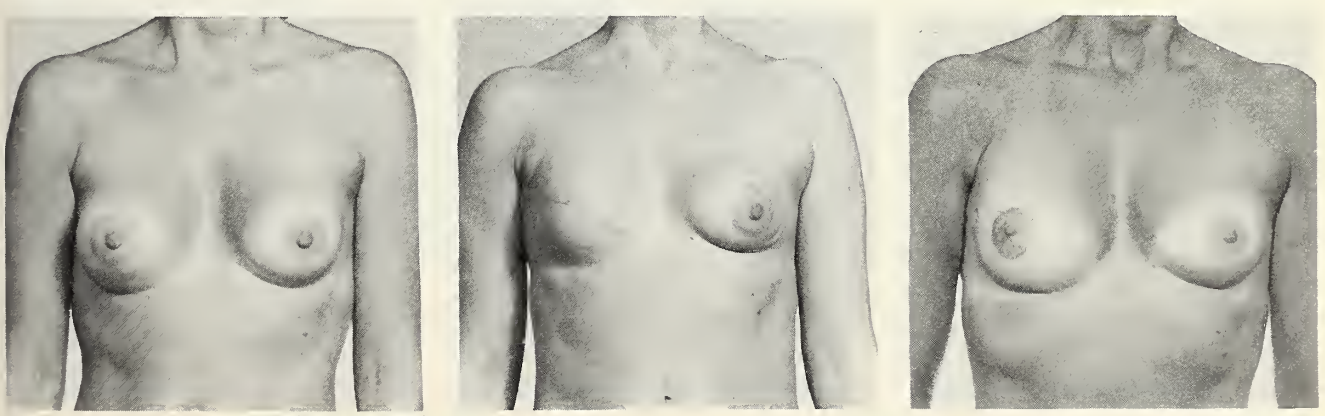


Figure 1. *Left: Preoperative view of a 40-year-old patient who underwent a right modified radical mastectomy for florid intraductal papillomatosis with immediate insertion of a Silastic prosthesis. Middle: Six months postoperatively. Right: Postoperative front view of the patient after seven years. Nipple was reconstructed by "nipple sharing."*

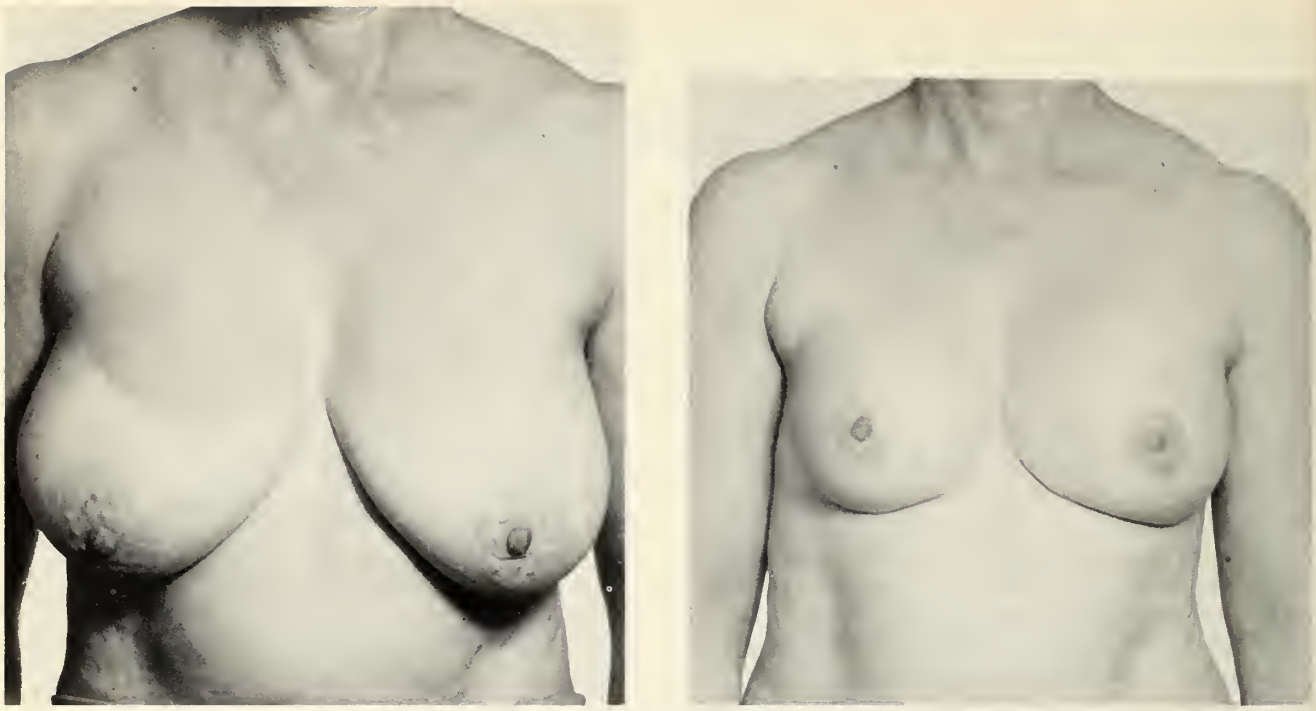


Figure 2. *Left: Preoperative front view of a 48-year-old patient who had intraductal carcinoma in the upper outer quadrant right breast. Right: Three years postoperatively. She had a right modified radical mastectomy, "immediate" reconstruction and left subcutaneous mastectomy with implant.*



Figure 3. *Left: A nine month postoperative view of a 31-year-old patient who had had a left modified radical mastectomy for adenocarcinoma with immediate insertion of a Silastic prosthesis and a right subcutaneous mastectomy with insertion of a Silastic prosthesis. Right: A postoperative view three months later following reconstruction of the nipple by nipple sharing and a groin graft for construction of the areola.*

using a full thickness skin graft from the groin which offers the best color correlation with the normal areola. The nipple is constructed either using a local flap, which is later tatooed for color coordination with the opposite nipple, or removing a portion of the opposite nipple and nipple sharing.



Figure 4. *Left: Preoperative front view of a 41-year-old patient with carcinoma of the right breast. Middle: She had a modified radical mastectomy for intraductal carcinoma with immediate insertion of a Silastic prosthesis; a four month postoperative front view. Right: A one year postoperative reconstruction front view of the same patient. A subcutaneous mastectomy was carried out on the left breast.*

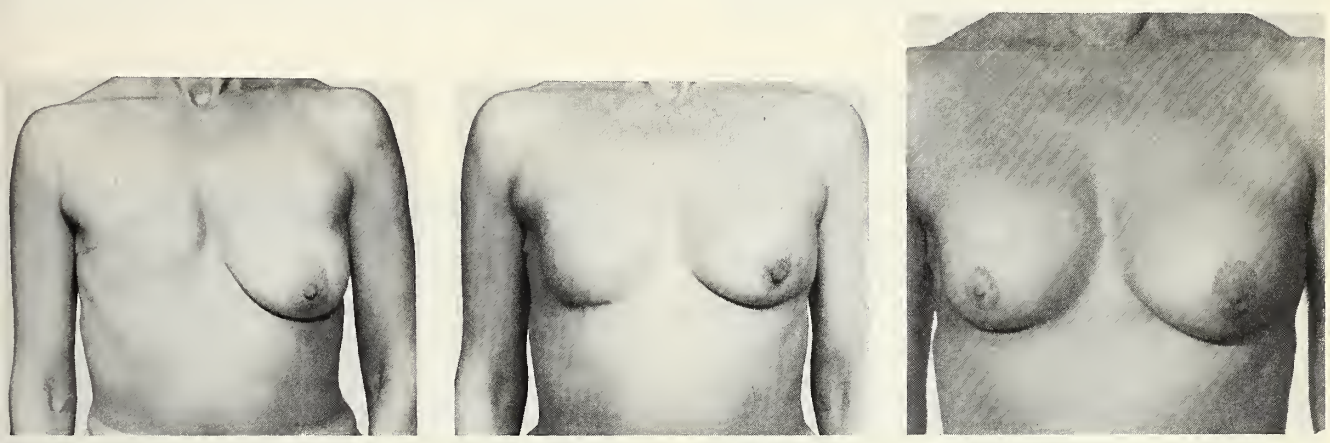


Figure 5. *Left: Preoperative front view of a 46-year-old patient who had a right modified radical mastectomy a year previously for tubular carcinoma of the breast. Middle: A seven month postoperative front view of the same patient following insertion of a Silastic prosthesis in the right breast mound and a subcutaneous mastectomy of the left breast with insertion of a Silastic prosthesis. Right: A postoperative front view of the same patient seven years following reconstruction.*



Figure 6. *Left: A preoperative front view of a 49-year-old patient who had a modified radical mastectomy performed four years previously for infiltrating ductal carcinoma followed by cobalt treatment. Middle: Five months following transfer of a right latissimus dorsi pedicle flap and a left subcutaneous mastectomy with insertion of a Silastic prosthesis. Right: Ten months following initial surgery and reconstruction with local nipple flap and a groin full thickness skin graft for areola.*



Figure 7. *Left: 35-year-old patient with resection of pectoral muscle and modified radical mastectomy. Middle: Creation of a large rectus abdominus musculocutaneous flap and preparation of breast site for transfer. Right: Postoperative appearance of one stage breast reconstruction, "tummy tuck" and later creation of nipple and areola.*

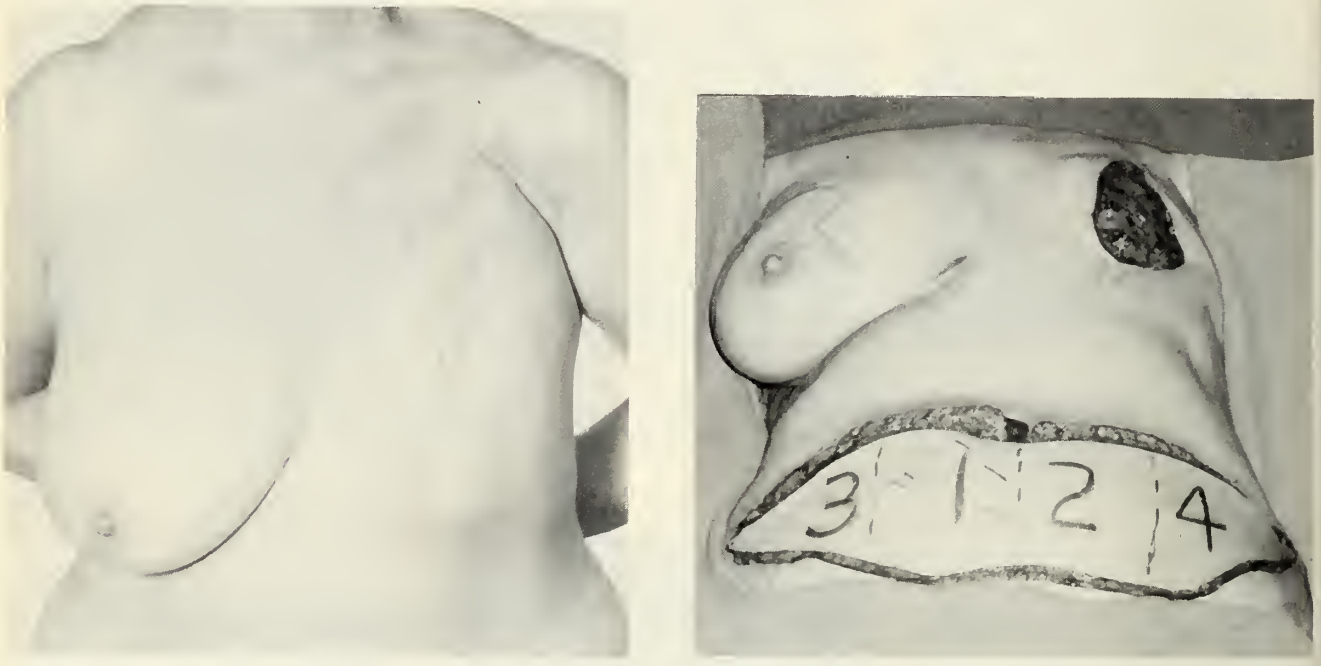


Figure 8. *Above left: A preoperative front view of a 53-year-old patient who had a left radical mastectomy seventeen years previously for infiltrating ductal carcinoma. Above right: The large abdominal rectus myocutaneous flap necessary to construct the large chest and axillary deformity is shown. (Opposite page.) Top left: Transfer of the myocutaneous flap from the abdominal area. Top right: A seven-month postoperative view of the same patient following reconstruction of left chest defect and right subcutaneous mastectomy.*

Summary

Breast reconstruction following mastectomy for carcinoma can be initiated immediately following the ablative surgery and during the same operative procedure. If reconstructive breast surgery is deferred for reasons such as chemotherapy or desire of the the patient, the initial reconstructive procedure can be instituted at any time by one of the techniques previously described.

Evaluation of our patients in this large series has failed to demonstrate that reconstructive surgery in any way affected the course of the patient's initial disease.

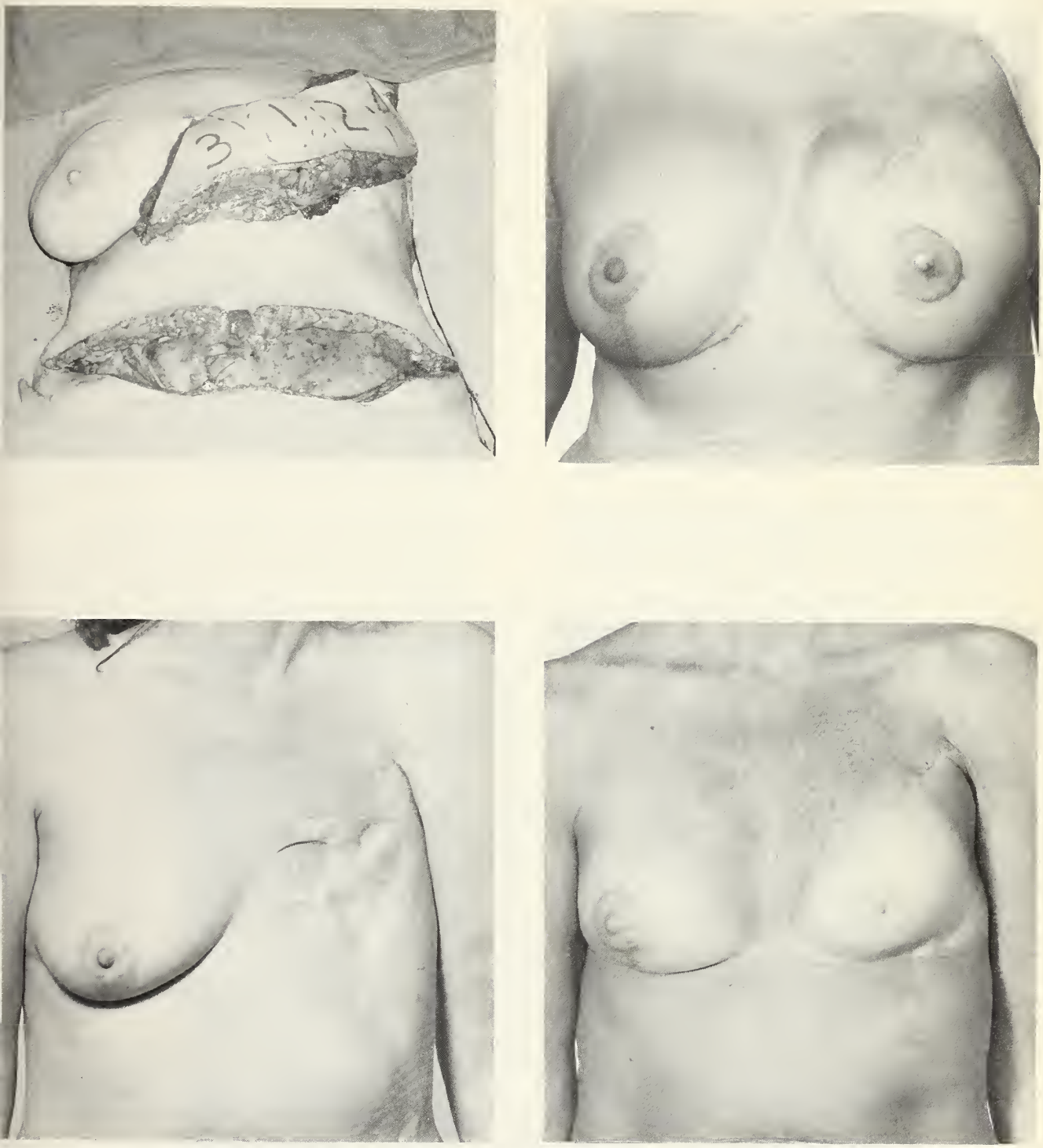


Figure 9. *Left: Preoperative front view of a 45-year-old patient who had a left radical mastectomy with right split thickness skin graft two years previously. Right: A 2½ year postoperative front view. The left breast was reconstructed utilizing a latissimus dorsi musculocutaneous free flap to resurface the chest area. Following this a Silastic prosthesis was placed in the subpectoral subserratus position. A left subcutaneous mastectomy was performed with simultaneous insertion of a Silastic prosthesis. The nipple was reconstructed by nipple sharing and the areola by utilizing a full thickness groin graft.*

Delegate Report From the AMA Meeting

John Glasson, M.D.

THE American Medical Association House of Delegates, meeting in Los Angeles between December 1 and 7, 1983, considered some 60 reports from the Board of Trustees and Councils plus 128 resolutions submitted by state delegations, individual delegates, medical specialty societies, and section councils of the American Medical Association.

The delegates received, in advance, approximately 50 resolutions and had submitted to them at the meeting an additional 78 resolutions which had been forwarded predominantly from the section on hospital medical staff, resident section and student section which met in Los Angeles immediately prior to the House of Delegates meeting.

The Hospital Medical Staff Section of the American Medical Association, meeting for two days immediately prior to the opening of the AMA House of Delegates, was again noteworthy as a breath of fresh air at the AMA meeting. In this section, some 700 physicians who are AMA members and who have positions of responsibility on hospital medical staffs throughout the nation, met in a formal House of Delegates format, now known facetiously in the AMA as "The Big House." Their deliberations were concerned primarily with three big issues.

First, consideration of the current changes in reimbursement of hospital services now being implemented by the Health Care Financing Administration. The hospital medical staff delegation from New Jersey was particularly concerned about the relationship between physicians and hospitals. They introduced several resolutions aimed at having the AMA assure by policy that aberrant physician profiles of practice as they affect economics should not be construed as adequate cause for withdrawal of privileges to practice in our hospitals.

Their second concern was that hospital medical staffs be given maximum responsibility for control of medical practice, even though ultimate control was determined to rest with hospital Boards of Trustees.

The third big question considered was the matter of the rewriting of the medical staff section of the Joint Commission on Accreditation Standards for Hospitals. Even though the hospital medical staff section voted to go back to the drawing board and start over, the ultimate action by the AMA House of Delegates favored a final resolution introduced by the Alabama state delegation. The provisions of this resolution became the basis for an amendment introduced by the AMA members of the Joint Commission on Accreditation of Hospitals so that the section involved reads as follows:

1. Individuals granted the privilege to admit patients to inpatient services are members of the medical staff. *Individuals are granted the privilege to admit patients to inpatient services in accordance with state law and criteria for standards of medical care established by the individual medical staff.* When nonphysician members of the medical staff are granted privileges to admit such patients, provision is made for prompt medical evaluation by a qualified physician for all such patients. This requirement for prompt medical evaluation by a qualified physician does not apply to qualified oral surgeons who have been granted the clinical privileges to perform a history and physical examination.

The wording for the Medical Staff Section created more correspondence between members of the N.C. Medical Society and its AMA delegates than any other issue, and we of the delegation appreciated hearing from our membership on this and other matters prior to the meeting.

The House of Delegates gave final approval to changes in the Constitution and Bylaws providing the addition of a resident physician to the AMA Board of Trustees as a voting member and the addition of a medical student to the AMA Board of Trustees as an ex-officio non-voting member. We in North Carolina are particularly proud of the fact that two North Carolina medical students, Al Osbahr and Keith McManus, are among the three medical students from the entire U.S. who were nominated as possible student members of the Board of Trustees.

The House of Delegates, in considering the matter of indemnity payments provided by insurance policies, rather than payments under the usual customary or reasonable concept which has for so long been the official policy of the AMA, reported the concept of multiple availability of types of payment depending on individual situations rather than the total abandonment of the UCR concept.

Also accepted, and of considerable general interest, was the Council on Medical Service report on standards for schedules of coverage provided employees under self-insurance programs.

A report by the Council on Scientific Affairs on recommendations for screening for breast cancer produced considerable controversy and discussion on the floor of the House but was eventually passed by a small margin. It is a rather thorough discussion which continues to support mammography as the best screening method available but goes into useful specifics regarding the value of self-examination for breast cancer.

Also very challenging were the reports and recommendations of the Council on Scientific Affairs for Hospitals as regards control of smoking in hospitals and a related resolution calling for the American Medical Association to promote the development of a smoke-free AMA staff by the year 2000.

In other actions, the House received an excellent report from the Council on Scientific Affairs on exercise for the elderly and from the Council on Medical Education on the availability of residency positions in the first post graduate year following medical school, indicating that available positions are now adequate at this level of training.

The House received and approved a report opposing the concept of surrogate motherhood and, in a timely action, also passed a resolution opposing the federal role in the so-called "Baby Doe" cases and supporting the right of parents and physicians locally to make final decisions in the case of severely handicapped infants in their medical management.

In an overwhelming vote by its House of Delegates, the American Medical Association has called for a narrowing of the use of the insanity defense in criminal trials.

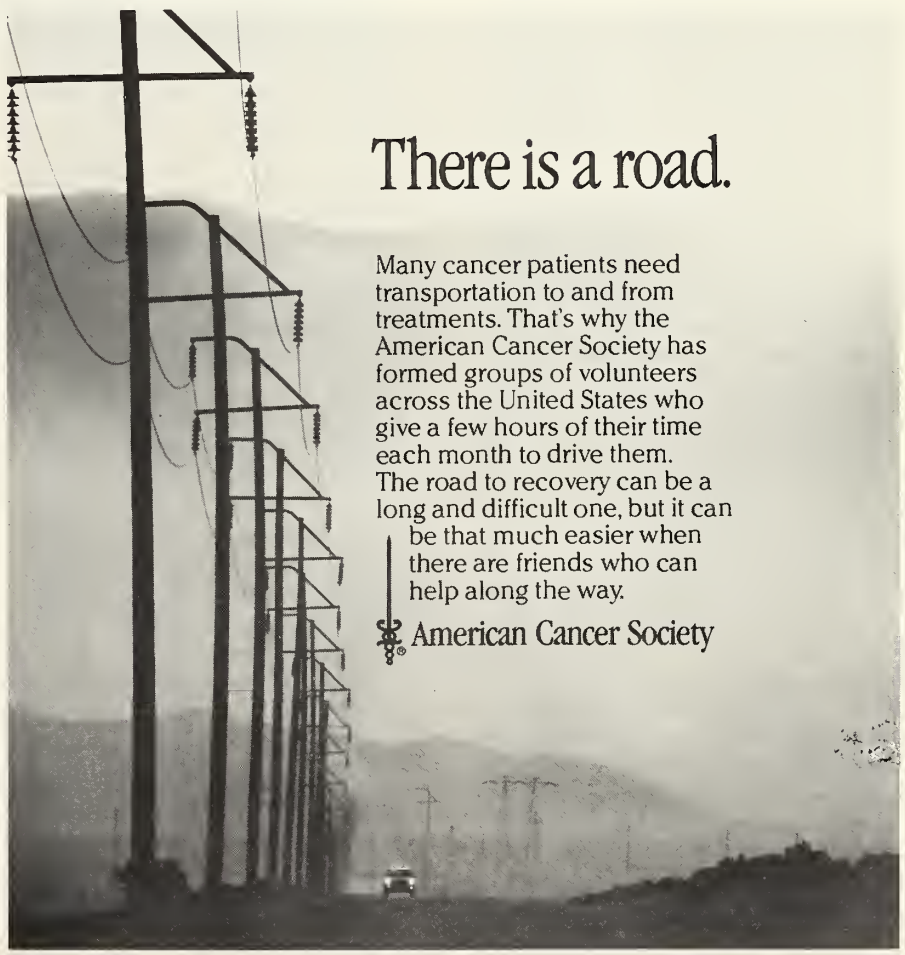
The report calls for replacement of the conventional insanity defense with statutes that would permit a defendant to be acquitted on insanity grounds only if the mental disease prevented him or her from committing the criminal act with the requisite state of mind, or mens rea.

Currently, most jurisdictions use the more conventional definition of insanity, which permits criminal defendants to plead insanity and be acquitted by providing evidence that at the time of the crime, the defendant lacked the capacity either to appreciate the criminality of his conduct or to conform his conduct to the requirement of the law.

The AMA is the first national organization to have adopted a policy calling for the narrowing of the insanity defense.

In addition to adopting the report, the delegates also agreed to continue collaborative efforts with the psychiatric and bar associations in an attempt to achieve a common policy position concerning the insanity defense.

The members of the Delegation particularly appreciated many comments received following the report on indemnity insurance payments published in the *North Carolina Medical Journal* (September 1983, page 577), as well as letters regarding other matters to be considered by the American Medical Association House of Delegates. We encourage more of this from all our North Carolina Medical Society members when future issues in medical care come to their attention.



This space contributed as a public service.

James Bell Bullitt, M.D., 1874-1964: A University of North Carolina Medical Giant

John Borden Graham, M.D.

The University of North Carolina recently dedicated the Preclinical Educational Building on the Chapel Hill campus to Kenneth Brinkhous and to James Bell Bullitt. Dr. Bullitt was one of the four great leaders of the School of Medicine in the first half of the twentieth century, the others being Isaac Hall Manning, Professor of Physiology; Charles Staples Mangum, Professor of Anatomy; and William de Berniere MacNider, Professor of Pharmacology. Those four men charted the course and fought hard for the four-year medical school. Dr. Bullitt felt so strongly about this that he created an endowment fund to help support a four-year school and placed his own funds into it.

Dr. John Graham, one of his students, writes down some of his memories of the North Carolina giant.

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I want to share with the readers of the *North Carolina Medical Journal* my thoughts of Dr. James Bell Bullitt. I was very fond of him, and he had an important influence on my life. In fact he served *in loco grandparentis* to me as I shall recount, although I doubt that he was aware of it.

Dr. Bullitt was born in Louisville, Kentucky in January 1874, 110 years ago, and lived to the age of 90, dying in March 1964. He was Professor of Pathology here from 1913-46 and served an additional 18 years as emeritus elder statesman, counselor, and friend of the Department and School. He came to his office almost daily until his final illness began two years before his death.

Dr. Bullitt belonged to a large family which has played an important role in the affairs of the state of Kentucky and of our nation. One of his great-grandfathers was Louis Marshall, the younger brother of John Marshall, the great Chief Justice of our Supreme Court. Justly or not, Louis Marshall, who was studying medicine in Paris during the French Revolution, was imprisoned for several years for "revolutionary activities." After his release Dr. Marshall practiced medicine in Kentucky and was later president of both Transylvania University and Washington College, now Washington and Lee University. Dr. Bullitt's brother, William M. Bullitt, was for many years an important figure in Kentucky politics and served as Solicitor General of the United States in the Taft administration. A cousin, William C. Bullitt, was the first American Ambassador to the Soviet Union in the late 1930s.

After his early education at Rugby Preparatory School in Louisville, Dr. Bullitt enrolled at Washington and Lee, then at Charlottesville in Virginia. His education occurred at the time when Cardinal Newman's "Idea of the University" was the American ideal, graduate education of the German type having only just been introduced at Johns Hopkins and Chicago. Newman's dictum, *mens sana in corpore sano,* was Dr. Bullitt's creed. In modern idiom, he was a man of high intelligence who tried to remain physically fit all his life.

Another influence which must have shaped Dr. Bullitt's outlook was the four years spent at Washington and Lee not long after General Lee's presidency. In the South at that time Lee's ideals — real and imaginary — were regarded as the hallmark of a gentleman. These included courtesy, kindness, thoughtfulness, and an elevated view of womanhood which seems very odd to us today. (Another W & L graduate, Tom Wolfe, has referred to this view of women as the "Myth of the Ice Goddess.") Generations of medical students referred to Dr. Bullitt affectionately and respectfully as "Gentleman Jim."

He was a life-long athlete. He played football at Washington and Lee and I think I remember his telling me that he was also on the football team at Virginia while a medical student. Although he played line-backer and full-back, he was not a large man. But American football was a different sport at the turn of the century, more like English rugby than armored warfare. My father, for instance, weighed only 118 pounds when he was All State quarterback at Davidson in 1910. Dr. Bullitt's appearance was that of an athlete. He walked with a firm step and stood straight as a ramrod as long as I knew him.

I first encountered Dr. Bullitt as a second-year medical student in 1939 when I was 21 and he was 65. My class was the first to study pathology in the "new" medical school building — now MacNider Hall. On the first day of class, we were met by a dignified and erect gentleman who appeared to be of middle age and who gave us detailed instructions on how to conduct ourselves in his course. The equipment in his new teaching laboratory included a new type of stool whose height could be adjusted and which swiveled 360 degrees. Wishing to be certain that everyone understood how to use it, Dr. Bullitt placed one atop the bench behind which he was to lecture, hopped up on the bench top, and spun himself around. We were dumbfounded, astonished both at the agility of this elderly gentleman and at the dignity with which he conducted himself.

From the Department of Pathology, University of North Carolina, Chapel Hill 27514.



Dr. Bullitt as captain of the football team at Washington and Lee University in 1894.

He always possessed complete aplomb, and I never once observed him to show a trace of self-consciousness.

Ten or fifteen years later, when Dr. Bullitt was now retired and must have been in his late 70s, I remember a conversation in the hall of MacNider with him and another person, possibly George Penick. We were discussing the importance of physical fitness. Dr. Bullitt insisted that it was a life-long matter and made his point by plopping down on the floor, salt-and-pepper grey suit and all, and proceeded to do five pushups. I am sure he would have done 25 had his astonished colleagues challenged him.

In conversation Dr. Bullitt spoke clearly, steadily, and at sufficient length to leave no uncertainty about his meaning. He joked about his loquacity and told a story on himself about a lengthy examination in college. Essay questions were normative in the 1890s, and Washington and Lee permitted unlimited time to respond. He wrote for seven hours on an examination and made a good grade, but his instructor requested that he come by for an interview. It consisted of a series of questions and answers.

"Are you from Kentucky?" "Yes."

"Are the women beautiful there?" "They seem to be."

"Are the race horses fast?" "They are said to be."

"Is the whiskey good?" "I suppose it is."

"Do you think, Mr. Bullitt, that it would be necessary for you to drink a whole barrel of whiskey to make a decision?"

I had conversations with Dr. Bullitt about many things, including financial matters. Two stand out in my memory. Both illustrated his belief that rational acts speak for themselves and require no explanation or apology. Dr. Bullitt believed strongly in husbanding his resources against adversity, having lived through at least three severe financial depressions. He pointed out that a well-known weakness of others was spending large amounts of money on unessential things such as expensive clothing. He said that he spent as little on clothing as would allow him to continue to be regarded as dignified. He explained that a man really needed only two suits of clothes if both were approximately alike and of moderately dark hue. One could be worn while the other was at the cleaners. He preferred a salt-and-pepper grey pattern because it did not show stains as readily as a solid pattern. A suit could be worn for many years if it was kept neat and clean, and no one would be aware whether it was old or new. An old one could be replaced by a new one, and no one would be the wiser. I don't know whether Dr. Bullitt actually practiced this policy because I never knew when he was serious and when he was pulling my leg. I wish that I knew, however, because the clothing scheme had obviously been very carefully thought out and had much to recommend it.

On another occasion he told me a story about a stock market deal. Again, I don't know whether the story is true or apochryphal, because I heard it in almost the same words in a Broadway play several years later. Dr. Bullitt stated that at the depth of the Great Depression in 1932 he decided that the country was either going to the dogs or would completely recover. Stock prices were at rock bottom, General Motors, General Electric, Standard Oil, etc. selling for less than $5 a share. If the country were to disintegrate, he would probably not have to repay his debts. If the country were to recover, he could make a lot of money by investing in stocks. So he went to Durham, borrowed all the money that Mr. John Sprunt Hill would lend, and bought blue chip stocks. He told me this story shortly after I joined the faculty in 1946, by which time such stocks should have divided several times and probably were quoted at $25-50 a share. Although he never stated that the financial problems of his retirement had been solved by this astute piece of business, such a move would have been completely consistent with his rational approach to life and his decisiveness when action was needed. If the story is correct, it was a very wise move on Dr. Bullitt's part because at his retirement in 1947 the University had not yet developed a pension plan for its faculty members.

When I took Dr. Bullitt's pathology course, it was tough but it was taught in a very simple and straightforward manner. We read the textbook of William Boyd, following his outline chapter by chapter. Our readings were supplemented by Dr. Bullitt's daily lectures, demonstrations of the day's slides on the projector by Dr. Russell Holman, autopsies performed at Watts Hospital at any time of day or night by Dr. Fred Patterson, and Dr. Bullitt's dreaded unknown slides.

Dr. Bullitt was an incredible lecturer. He would appear on the dot of the hour dressed in his grey suit, reach into his left inside jacket pocket and pull out a small set of 3x5 cards. He would turn to a spot marked by a paper clip, place



Portrait of four great leaders of the UNC School of Medicine in the first half of the 20th century. From the left: Charles Staples Mangum, Isaac Hall Manning, James Bell Bullitt, and William de Berniere MacNider.

it in front of him and start talking. He would talk steadily for exactly 40 minutes, put the paper clip at the point he had reached, replace the cards in his pocket, and answer questions. He went through this exercise without apparent effort for two semesters, touching on the major points and illustrating them with anecdotes, many of which dated back to his years in Mississippi. We thought that most of his stories were probably fabricated, because they fitted so neatly into his subject matter; but in any event they were memorable and anything might have happened in Mississippi.

Thirty or so times a year, Dr. Bullitt exposed us to unknown slides, and we played the game of unknowns by very strict rules. Exactly 30 minutes were devoted to the examination of a slide and the writing of a 50-word description of the tissue and the diagnosis. If one did not finish on time, or if the description contained more than 50 words, and "F" was awarded.* This exercise forced students to develop an unusual writing style, one which might be referred to as "Bullitt-English," a form of pidgin English. A paragraph of the approximately correct length was written and the words were carefully counted. Then the paragraph was reduced to exactly 50 words by deletion of a sufficient number of articles and prepositions. Dr. Bullitt must have suffered from having to read these strange paragraphs, but he retaliated with trick slides, fabricating impossible tissues. We found several of these unknown slide sets after his death. I remember one which consisted of a piece of human liver into which he had inserted the retina of an eye. Since identification of the tissue was the first step in diagnosis, this must have caused much head scratching. I also remember an unknown given to my class with the statement that the tissue had been obtained from a man found dead in bed in Hillsborough. The tissue proved to be from the pancreas. After spending 30 minutes searching unsuccessfully in my textbook for a pancreatic disease which might have caused sudden death, I gambled in desperation on "acute pancreatitis." When Dr. Bullitt returned the graded papers, he explained that the pancreas was in fact normal and that sudden death had resulted from having been hit on the head with a hammer while asleep.

Dr. Bullitt influenced me in other ways. He convinced me that I should smoke a pipe rather than cigarettes, and he taught me wood carving. He pointed out that even cheap pipe tobacco could be made smokeable by humidifying it in a canister which contained an apple. I learned from him about "Old Crop" which was sold at Shields' grocery store on Franklin Street and was dispensed in a cloth bag at $1 a pound. I shudder to think how my colleagues and family must have suffered during the 15 years I smoked "Old Crop." But woodcarving was innocuous and great fun; it

* A student later to become a prominent surgeon chronically failed to observe this rule. He flunked Pathology and was required to repeat the entire second year. He never again spoke to Dr. Bullitt after having passed the course on the second try.

even prevented me from going insane with boredom at a later point in my career when it became necessary to spend long hours in committee meetings.

Dr. Bullitt carved and polished his wood objects wherever he was, the polishing being particularly obvious at faculty meetings. He was quite unselfconscious about where he did his polishing, because the carvings had to be polished somewhere, and what else could one do at a faculty meeting? The wood polishing led the students to spoof Dr. Bullitt in one of the Student-Faculty Day skits by presenting a mock meeting of the Pathology department in which the student playing Dr. Bullitt would turn on a floor-polishing machine every time the student playing Dr. Brinkhous tried to speak. But Dr. Bullitt was really very thoughtful; he used only fine grain sandpaper at faculty meetings.

He was unfailingly courteous, kind, and thoughtful, and loved children. My children adored him and remember him with great affection. Whenever he saw them at departmental parties or in the halls of MacNider, he always stopped to speak, following which he would toss them high in the air. They remember him as tossing them without removing his pipe from his mouth. They thought that, like Popeye, it was part of his face.

Student Aid was a very small operation at Chapel Hill before World War II and many medical students were on very tight budgets. Dr. Bullitt was known to be always good for a loan when every other possibility had been exhausted. No one knows how many loans he made, but he told Miss Dunlap, the Dean's secretary, that every loan he had ever made had been fully repaid, except one.

Dr. Bullitt was a life-long patriot. He had been a medical officer in World War I and I am certain tried to enlist when World War II began. Since he was in his late 60s and could not be accepted for military duty, he volunteered for the Red Cross, becoming the teacher of first aid for patriotic local ladies. Mrs. Berryhill remembers with amazement watching Dr. Bullitt teach resuscitation to the dignified ladies of the community under circumstances which would have been very amusing had first aid not been such a deadly serious matter to them.

Gasoline was tightly rationed during World War II and Dr. Bullitt had a serious problem. He liked to go home for lunch, but four trips a day from Gimghoul Road to MacNider were too time-consuming on foot and a car required too much gasoline. So naturally he bought a bicycle. Dr. Bullitt on his bicycle — fully dressed, pipe in mouth, hat on head, clips on his ankles, and accompanied by a small beige dog — was an unforgettable sight in Chapel Hill during the war. Unfortunately no one seems to have taken a picture of him in full flight although there is a snapshot of him booted and spurred preparing to ride. At the war's end the increase in auto traffic caused Mrs. Bullitt to become very worried about his safety. She wanted him to give up the bike, but Dr. Bullitt had by now become very attached to bike riding, and it almost required an act of the Legislature to get him to stop.

I think Dr. Bullitt regarded George Penick and me as wild-eyed radicals when we returned to the University from World War II full of one-worldism and sympathy for the downtrodden. George was especially suspect because his



James Bell Bullitt.

father was the bishop of Dr. Bullitt's diocese and the Bishop was thought to hold very advanced views about social issues. We had many arguments about social welfare, racial integration, the atomic bomb, and other important topics of the day. Neither side budged an inch, because all of us were very stubborn, but we always ended our arguments on a friendly note, prepared to stonewall again the next day.

Dr. Bullitt was the most thoughtful of men and in his later years was waited upon by an attentive group of ladies in the medical school whom Mrs. Bullitt referred to as his "harem." Dr. Margaret Swanton, Miss Sara Virginia Dunlap (the Dean's secretary) and Miss Mittie Pickard, his long-time technician, were the frequent recipients of flowers from his garden, or small gifts, and he never forgot their birthdays. They in turn were equally solicitous of him. Miss Pickard, unfortunately, has died but if she were alive and here today she would be sharing in this appreciation. I would expect, however, that she would take me off to one side and chew me out for not having said things exactly the way she remembered them.

Dr. Bullitt appeared in the Department daily until he entered a nursing home in 1962. This was the same year that we occupied the northern extension of MacNider Hall, now known as the Research Wing, and about a decade before we moved into the building we recently dedicated to Dr. Bullitt and Dr. Brinkhous. I have wondered what Dr. Bullitt would have thought of our Preclinical Educational Building. It is tall and one's colleagues are scattered among nine small floors. We have learned that departmental col-

legiality is greatly impaired when departmental housing is arranged this way. I know that Dr. Bullitt would have disliked this very much, because he loved to wander around the halls in MacNider inquiring about our welfare and striking up conversations. But Dr. Bullitt always took the rational approach. Looking at all sides of the question, he probably would have opined that a nine-story building connected by eight flights of stairs is not the best arrangement, but it has at least one redeeming feature. One can remain physically fit by running up and down the stairs!

Dr. Bullitt was a member of the medical faculty, active and emeritus, for more than 50 years. This places him in a very small and select group. The group includes Dr. MacNider, his contemporary. It is very fitting, therefore, to those of us who knew them both that the building bearing Dr. Bullitt's name be adjacent to the one that bears the name of Dr. MacNider.

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Before prescribing see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING
This dru[illegible] indicated for initial therapy of edema or hyperte[illegible] edema or hypertension requires therapy titrate[illegible] individual. If this combination represents the do[illegible] determined, its use may be more convenient in pa[illegible]anagement. Treatment of hypertension and edema [illegible]atic, but must be reevaluated as conditions in each [illegible] warrant

[illegible]raindications: Concomitant use with other potassium-[illegible]ring agents such as spironolactone or amiloride. Further use [illegible] anuna, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

Problems and Prospects for the "Living Will" in North Carolina

John C. Moskop, Ph.D.

JUDGING from the frequency of its revision, North Carolina's Natural Death Act[1] remains a controversial piece of legislation. Since its enactment in 1977, each subsequent session of the General Assembly (in 1979, 1981, and 1983) has seen fit to revise portions of it. Critical reviews of the Act and its amendments have appeared in the state's medical and legal literature.[2-5] Each of the three revisions has improved the Act in important ways. The 1979 revisions recognized the crucial distinction between *allowing* a patient *to die* and determining that a patient is *dead* on the basis of irreversible cessation of total brain function. The 1981 revisions broadened the Act to provide a legally sanctioned mechanism for *withholding* (in addition to discontinuing) extraordinary treatment from *mentally incapacitated* (in addition to comatose) patients.[4] The 1983 revisions further refined this mechanism, reducing the number of physicians required to confirm the patient's condition and providing that extraordinary means may be withdrawn or withheld *with the concurrence* of, rather than *at the request* of, the appropriate relative or guardian.[5]

The second and longest section of the Act is its "living will" clause. This clause specifies a mechanism for executing a "Declaration of a Desire for a Natural Death" and shields physicians from criminal or civil liability for honoring such a declaration. Judging from conversations with and observation of physicians who care for the terminally ill, however, the number of persons who have prepared and signed a "Declaration of a Desire for a Natural Death" remains quite small. Because the law has not been widely publicized or promoted, failure to use the "living will" clause may simply be due to lack of knowledge about it. If this is the case, as more and more people learn about the law, more will take advantage of it. Some of those who are already familiar with it, however, are still reluctant to sign a "living will," even though they have no desire that their own lives be prolonged in the sad and hopeless condition that medical technology sometimes permits. In this article, I will suggest some reasons for their reluctance and recommend a different approach in which a person designates some*one* in advance to make treatment decisions for him when he is no longer able to do so. This approach has recently been reviewed and endorsed in a report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.[6]

From The Humanities Program, East Carolina University School of Medicine, Greenville 27834.

The North Carolina Natural Death Act

To begin, let us consider what a person authorizes when he prepares and signs a living will document according to the North Carolina Natural Death Act. The Act recognizes the following form as specifically determined to meet its requirements:

Declaration Of A Desire For A Natural Death

I, _____, being of sound mind, desire that my life not be prolonged by extraordinary means if my condition is determined to be terminal and incurable. I am aware and understand that this writing authorizes a physician to withhold or discontinue extraordinary means.

This the ____ day of _____.

Signature _____[7]

With this document in force, if the person's attending physician determines that his or her condition is terminal and incurable (and that determination is confirmed by another physician), the attending physician may, without fear of criminal or civil liability, direct that extraordinary means be withheld or discontinued. Extraordinary means are defined as "any medical procedure or intervention which in the judgment of the attending physician would serve only to postpone artificially the moment of death by sustaining, restoring or supplanting a vital function."[8]

In short, executing this declaration authorizes one's attending physician to withhold or discontinue treatment in a certain situation, namely, when one's condition is terminal and incurable and the treatment would only artificially postpone death. The document gives substantial discretion to the attending physician, since he or she must judge not only when the patient's condition is terminal and incurable (subject to confirmation by another physician) but also which treatments would only prolong life artificially. Because the key words "terminal," "incurable," and "artificial" remain undefined in the statute, it falls largely to the attending physician to interpret the situation and make a treatment decision according to his own understanding of these broad and rather vague concepts. Unlike several other states, North Carolina specifies no penalty for a physician who fails to carry out a written declaration. This may be viewed as a weakness by some, but in view of the very general language of the declaration and the substantial interpretation required by the physician, it would, I think, be difficult to show conclusively that a decision to continue treatment in a particular situation violated the declaration.

Is this a good mechanism for insuring that one's life will not be unduly prolonged (or shortened)? *If* I knew who

uld be the attending physician making decisions about prolonging my life *and if* I knew and trusted this physician's judgment about when life is not worth prolonging and when hope for a cure is not appropriate, *then* I would be inclined to say yes. In that case, I would be willing to let my physician decide when no further efforts should be made to prolong my life "artificially." There is, however, no way to guarantee that a particular physician will be there to care for me in the event of a terminal illness or injury. I may, for example, be injured while traveling far from home, or my personal physician may be away when my condition deteriorates. Moreover, some physicians I might otherwise choose to care for a medical or surgical problem are not people I would want to decide about what efforts should be made to prolong my life.

If, then, I execute a declaration according to the Natural Death Act, I authorize the physician attending me in a condition he or she judges to be terminal, whoever that physician may be, to withhold or withdraw "extraordinary" treatment. In order to act on my declaration the attending physician must, of course, know that it exists. Anyone, including myself, my family, or another member of the health care team may give him or her this information. Before acting on my declaration, the physician may choose to consult with my family, but the Act does not require this, and it protects the physician who acts in accordance with my declaration even if this is done against my family's wishes. If, in contrast, I have not signed a declaration, treatment may be withheld only with the concurrence of my spouse, guardian, or a majority of relatives of the first degree, in that order, if any of these are available.[9] It appears, therefore, that I ought to prepare a living will if I prefer that my attending physician, not my spouse, guardian or relatives, make the decision about withholding or withdrawing life-prolonging treatment, based on a general statement of my desires. I should not prepare a living will if I want to insure that my spouse, guardian or relatives play a significant role in making this decision.

In sum, the North Carolina Natural Death Act offers two procedures for decision-making regarding life prolonging treatment for the terminally ill. On the one hand, I may make a declaration stating my wishes in more or less general terms. This authorizes my attending physician to interpret my desires and honor my wish not to be treated in the general circumstances described. On the other hand, I may make no declaration, thereby leaving decisions about life prolongation to my physician and spouse, guardian or family, should I become incompetent.

Proxy Directives

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research has recently called attention to a third alternative for making decisions about the prolongation of life. According to this alternative, which the Commission calls a "proxy directive," a person designates someone else to make decisions regarding his or her treatment should the person become unable to make them. Two recently adopted natural death statutes (in Delaware[10] and Virginia[11]) explicitly recognize this alternative by providing for the appointment of a proxy or agent and recognizing the proxy's authority to make treatment decisions for the person who appointed him or her. In addition to these statutes, the Commission argues that durable power of attorney statutes existing in 42 states (including North Carolina[12]) may be used to make proxy directives.[6] Under these statutes, one person (the principal) may confer upon another (the agent or attorney-in-fact) the legal authority to perform certain acts on the principal's behalf, even after the principal is incapacitated or incompetent. Although these statutes were not enacted to facilitate health care decision-making, there is nothing to prevent the execution of a power of attorney for this specific purpose.

Appointment of an agent to act in one's behalf has several advantages over the more traditional versions of the living will. First, it allows the patient's agent to make specific decisions in response to specific developments in the patient's condition. The physician, therefore, is freed from the difficult task of trying to determine, based on only a very general statement of desires in a "living will," what the patient's wishes in a specific situation would be. (The physician, however, will remain responsible for insuring that the patient fulfills the provisions of the natural death statute, e.g., that he or she is in a terminal condition and has made a valid declaration.) Several commentators have viewed this imprecision and ambiguity as a major defect of the living will.[13, 14]

Second, a proxy directive allows a person to appoint someone he trusts implicitly (perhaps a spouse, a son or daughter, or close friend) to make these decisions for him, rather than rely on a physician he may know less well, or perhaps not at all. The person may also feel more confident in his or her agent's ability to choose the right course of action based on the agent's intimate knowledge of the person and a loving concern for his or her well-being.

The alternative of proxy directives is not without its own disadvantages. There may be practical problems, e.g., the procedure for executing a power of attorney in North Carolina is more cumbersome than that for executing a living will. This, however, is not the case in Delaware and Virginia, the states that have incorporated proxy directives into their natural death statutes. A second and potentially more serious problem is the possibility of abuse of the proxy's authority. Someone might, for self-interest or malicious reasons, pressure a person into appointing him or her proxy for making health care decisions. Alternatively, a person who had, in good faith, agreed to be a proxy might later be faced with a conflict between his own interests and those of the person who designated him proxy. In such instances, a proxy might make decisions contrary to the patient's best interests. Safeguards can be instituted to guard against this possibility, however. For example, the North Carolina Natural Death Act requires that two witnesses attest to the mental competence of the person signing the declaration and that a clerk of court or notary public further attest that the person executed the document willingly and voluntarily.[7] The Delaware and Virginia Natural Death Acts also circumscribe rather narrowly the kind of situation in which agents may be authorized to make treatment decisions for others. Furthermore, as in cases of child abuse, the physician is responsible to seek to override the

proxy's decision if that decision is clearly harmful to the patient.*

Conclusions

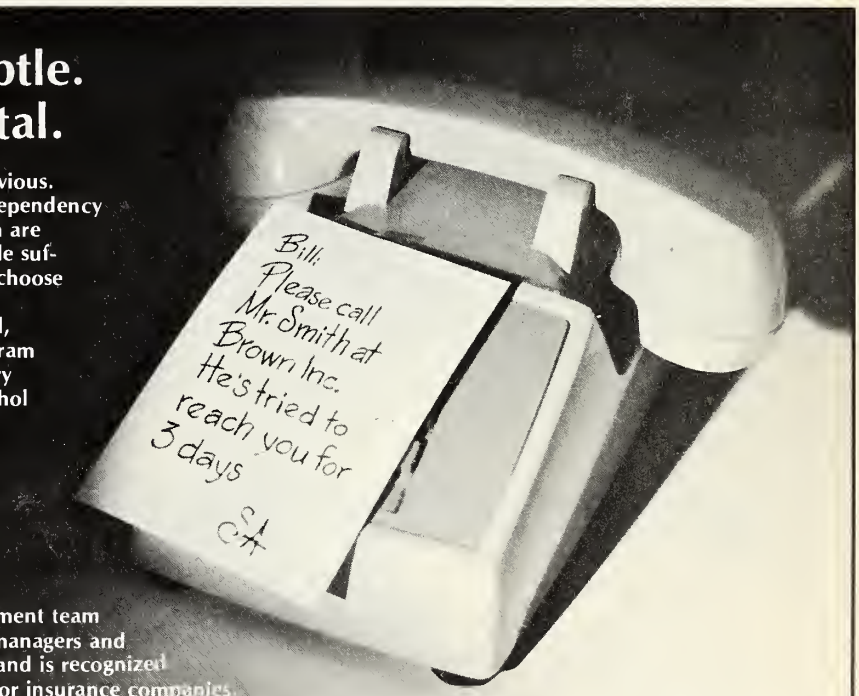
The generality of North Carolina's "Declaration of a Desire for a Natural Death" and the unavoidable uncertainty regarding who will interpret and apply it limit its usefulness as a means for honoring patients' preferences about life-prolonging treatment. A promising alternative included in several recent natural death statutes is the proxy directive, or designation of a person to make decisions regarding life prolonging treatment should one become incompetent. This alternative would give the patient a greater assurance regarding who would make these decisions for him or her. It would also allow treatment decisions to be made in light of the specific circumstances of the patient, thus avoiding the difficulty of trying to apply a general statement of desires to a complex situation. These are good reasons for considering yet another revision of the North Carolina Natural Death Act to recognize proxy directives for decisions about life-prolonging medical care.

* For this point I am grateful to Dr. Joanne Lynn.

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The signals may be subtle. The disease is often fatal.



In many fatal illnesses signs and symptoms are obvious. However, in other illnesses, like alcoholism and dependency on other drugs of abuse, signs of impending death are often subtle. Today, more than ever before, people suffering from alcoholism/chemical dependency can choose to live instead of dying from this epidemic health problem. Woodhill, a division of Appalachian Hall, offers a complete and comprehensive 28-day program for the person who chooses treatment and recovery over the consequences of continued abuse of alcohol and/or drugs. Located in the beautiful mountains of Western North Carolina, Woodhill provides detoxification, individual and group psychotherapy, education groups, psychodrama, weekly family involvement and a therapeutic activities program. Integration into Alcoholics Anonymous, Narcotics Anonymous and Al-Anon along with a comprehensive 12 to 24 month aftercare program is also provided. The Woodhill treatment team works closely with Employee Assistance Program managers and supervisors. Appalachian Hall is JCAH accredited and is recognized by Blue Cross, Champus, Medicare, and other major insurance companies.

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An Insight Into Utilization Review: Beyond Responsibility and Toward Accountability* (a mini history of the development and evolution of peer review)

Harold R. Silberman, M.D.

"THE Hospital exists in our society 'under a contract' that requires it to exercise reasonable diligence regarding the quality of medical care of all the patients all the time."

1919: Establishment by the American College of Surgeons (ACS) of its Hospital Standardization Program.

1940: ACS moved to actual review of patient care by tissue committees, followed quickly by antibiotic and later transfusion committees.

1965: Darling case adjudicated in Illinois *(Darling v. Charleston Community Hospital):* not the passage of a new law, but a Court's interpretation of society's position and the expanding responsibilities of hospitals as institutions, thus changing their relationships with staff physicians.

1965: Utilization review said to be required under Medicare with the focus on peer review.

1972 (early): American Hospital Association announced QAP, its Quality Assurance Program.

1972: Joint Commission on Accreditation of Hospitals initiated its TAP institutes (trustees-administrators-physicians) and informed hospitals as well as their medical staffs that they would be expected to control the quality of care if they were to be accredited.

1972 (late): Congress enacted Public Law 92-603. That act made the hospital itself responsible for the quality of its care and called into being Professional Standards Review Organizations (PSROs). Their mission: to determine for all patients treated under Medicare, Medicaid, and Title V of the Social Security Amendments whether the care was reasonable, medically necessary, of recognized (professional) quality, and provided in the proper facility.

> ". . . duty and function of each Professional Standards Review Organization . . . to assume . . . review of the professional activities . . . in the provision of health care services and items for which payments may be made (in whole or in part) . . . for the purpose of determining whether —
>
> (A) such services and items are or were medically necessary;
> (B) the quality of such services meets professionally recognized standards of health care; and
> (C) in case such services and items are proposed to be provided in a hospital or other health care facility on an in patient basis, such services and items could, consistent with the provision of appropriate medical care, be effectively provided on an out patient basis or more economically in an in patient health care facility of a different type." (PL 92-603 SEC. 1155) [A][1]

1974: PSROs in place and required under the Act to accept the hospital's efforts (through its several review committees) at monitoring services/care "to the extent that *they did the job in acceptable manner." (italics mine)*

1974-1982: Methodological problems brought changes and new vocabulary: concurrent admission (or preadmission) certification; concurrent continued-stay review of extended-stay cases; retrospective review; focused-out review (necessitated by financial constraints placed upon PSROs by federal funding cuts), etc., etc.

1982 (September): Peer Review Improvement Act of 1982 (sections 141 through 150 of Public Law 97-248, the Tax Equity and Fiscal Responsibility Act [TEFRA], enacted September 3, 1982) created a new Federal authority to fund utilization and quality control peer review organizations to be known as PROs. This new act replaces a 1972 amendment to the Social Security Act which created Professional Standards Review Organizations (PSROs). Part of this so-called TEFRA initiated prospective payments at a fixed rate until the next step.

1983 (April): PL 98-21 provides for a prospective payment concept that was implemented by the methodology of DRGs. Most hospitals began this approach by October 1, 1983, depending on the timing of their fiscal years.

When Congress passed prospective payment laws, it expressed its will that the Federal Government take a bold step to curtail rising hospital costs and to protect the solvency of Medicare for future generations.

1983 (October): Prospective payment, at "flat rate" per patient, replaced cost-based reimbursement system at Duke.

* $35 billion in public funds paid out each year under Medicare Part A to 7000 hospitals because of 350,000 physicians providing in-patient care to this country's elderly and disabled beneficiaries.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

In this climate, HCFA (Health Care Financing Administration) instructs PSROs to drop both review of whether ancillary services are appropriate and the traditional analysis of lengths of stay, advising instead assessment as to whether an admission is needed and where stay is excessively long or costly, PSROs are to review for *unnecessary care*.

1984 (July): Duke and some other hospitals with similar fiscal year dates begin prospective payment (partially −25% per case) for first year via a system of 467 diagnosis-related groups (DRGs).

1985: By this date, DRG legislation requires the Secretary of Health and Human Services to report on the "advisability and feasibility of applying DRGs to physician charges for hospital services and to recommend legislation to apply the DRG concept to physicians."

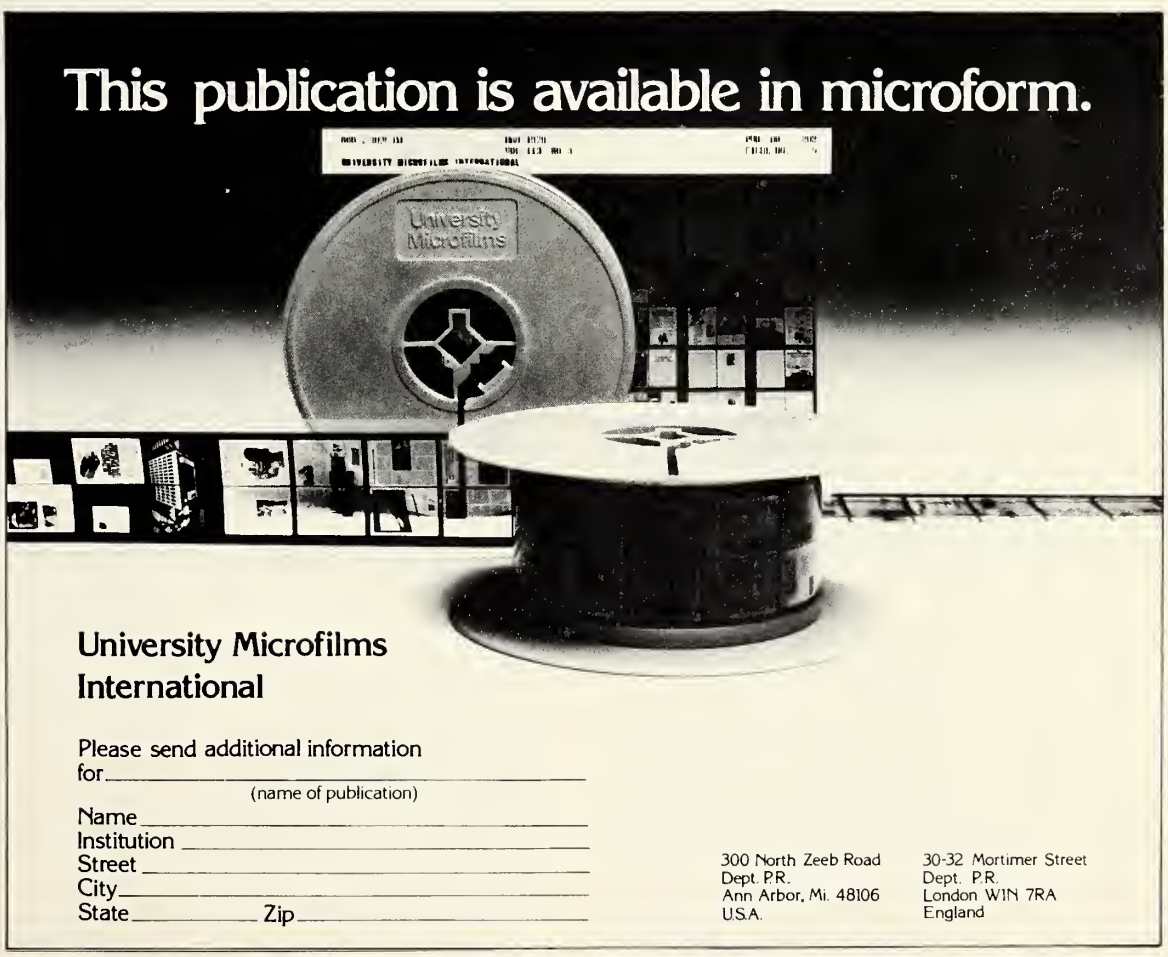
Again the key issue for review groups would be whether or not a hospital stay is really indicated.

1987: DRG rates should be fully phased in over the previous 3 years.

Educators know and are frustrated by the fact that auditing is not necessarily carried out for the purpose of adding to medical knowledge, but simply to see if current medical knowledge is being applied; and if not, why not and what can/must be done about it.

Hospitals must recognize that PSRO/PRO legislation does not alter the hospital's legal responsibility for review and maintenance of quality as established under statutory law and case law nor does it abrogate the requirements to comply with JCAH/AHA criteria for accreditation.

After considering the evolution to this state of affairs a physician might be more receptive to one writer for the Sounding Board column in the *New England Journal of Medicine* (Platt R: NEJM 1983; 309:726-730) "are we ready for these kinds of changes? Should we be? Perhaps we ought to be less concerned about cost containment and more prepared to spend 12 or 13% of the gross national product on health care by 1990. What we should not do is pretend that *painless* cost containment is an achievable goal."



An Encouraging Word on the Socioeconomic Front

William J. DeMaria, M.D.

LINCOLN County physicians were notified in December 1982 of a significant change in medical insurance benefits by a major employer in their county.

The company, Mohican Mills of FAB Industries, alarmed with their increasing costs of medical services, reviewed the utilization and cost data provided by their insurance carrier, Blue Cross and Blue Shield of North Carolina. It was agreed that an immediate and radical change in benefits was necessary if control of escalating costs was to be attained.

The new benefits package includes a $200 deductible for each hospitalization with a 60-day renewal period. There is a 100% usual, customary and reasonable payment not subject to deductibles for hospital and doctors' charges for outpatient treatment of accidental injury within 72 hours, outpatient treatment of medical emergencies within 72 hours, outpatient surgery, and outpatient diagnostic services. Reimbursement for inpatient services is at 80%, clearly providing an incentive for treatment on an outpatient basis whenever possible.

A preferred provider arrangement was made due to the presence of two hospitals in the community, a for-profit institution with average charges per day 79% greater than at a neighboring not-for-profit hospital. To encourage employees' use of the lower cost hospital, the inpatient deductible is only $100 for this preferred provider.

In addition, a pre-admission certification program was selected as an acceptable way of putting brakes on both the user and provider in an area where studies had shown that significant hospital overutilization existed. The pre-admission certification requires the physician's office to request certification for all elective admissions other than for emergency and obstetrical problems. Certification is accomplished by the physician's office calling a designated collect number at the Blue Cross and Blue Shield of North Carolina Service Center where registered nurses with physician consultant backup make the decision regarding reimbursement for elective admissions. The primary purpose is to encourage ambulatory surgery, decrease weekend admissions, conduct pre-admission studies in ambulatory settings and decrease admissions for routine studies which can be conducted in an ambulatory setting.

Results of the first six months are encouraging. The rate of hospitalization for these employees as measured in days per/1000 persons has decreased by a significant 20%. In addition, the preferred provider arrangement has resulted in approximately one-third fewer admissions to the high cost hospital in contrast to the same time period in 1982.

We present this note to encourage physicians in North Carolina to join private industry in developing cooperative programs which aim at slowing the disproportionate rise in health care cost. In addition, we wish to note formally that this successful introduction of pre-admission certification in North Carolina could not have been achieved without the cooperation of physicians in Lincoln County. We realize that physicians are reluctant to add yet another administrative step in conducting medical care for their patients. Increasing numbers of physicians do agree, however, with the need to demonstrate their willing cooperation in cost containment programs. These cooperative ventures are essential if integrity of private practice, quality of care, and coveted patient-physician relationships are to be maintained.

Among the dizzying and confusing events ongoing in the medical care arena, it is most reassuring to provide the *Journal*'s readers with an encouraging word.

From Blue Cross/Blue Shield of North Carolina, P.O. Box 2291, Durham 27702.

Medical Exorcism — Acute Dilantin Intoxication

Ronald B. Mack, M.D.

SEVERAL centuries before Christ, Hippocrates stated the brain was the organ involved in epilepsy; his fellow Greeks, however, believed that this disease was caused by supernatural forces. In the first monograph concerning epilepsy that we know about (entitled *The Sacred Disease),* Hippocrates publicly assailed the citizens of his country for believing that the disease was "sacred." He attacked the wizards, magicians, charlatans, et al. who, he said, hid their ignorance and fraudulent practices behind the cloak of the divinity of epilepsy.[1] Hippocrates believed that a generalized convulsion is always to be regarded as a serious omen until a thorough examination of the afflicted person and the passage of time have proved it to be but an incidental symptom of some transient or curable disease.

The theory that the body could be taken over by supernatural, malevolent forces was still very popular in the Middle Ages where it was widely believed that people's bodies could be inhabited by demons. Epilepsy (called the "falling sickness" in that period of history) was thought therefore to be due to demonic possession. It probably wasn't until the 19th century that reason entered the minds of clinicians when Jackson identified, in 1870, the cerebral cortex as the site of disturbance in epilepsy. Even in the enlightened 1980s there are some who view the epileptic as "unclean." Modern therapeutic modalities attempt, in a sense, to get rid of the "demons" that cause the "falling sickness."

Of the various chemicals used to exorcise an epileptic from his/her misery, *phenytoin* (Dilantin, formerly known as diphenylhydantoin — DPH) is one of the best known and prescribed anticonvulsants. The value of this drug in the therapy of epilepsy was first reported in 1938. Because of this drug's remarkable power and efficiency you might think that it would produce devastating effects if taken in overdose. In fact, fewer than 10 deaths have been reported in this country from acute or chronic phenytoin overdose from any route of administration. Accidental childhood overdose from this drug is surprisingly uncommon, considering its availability, and when it does occur is usually a relatively mild event.

In therapeutic doses, drug absorption is slow due to its limited solubility in the GI tract, and peak serum levels after a single oral dose occur in 6-12 hours. It takes 6 to 9 days of daily medication to achieve a steady-state condition. After absorption the drug is hydrolyzed by the liver, conjugated with glucuronide and excreted in the urine and bile. Less than 2% of this drug is excreted in the urine unchanged. The T½ (half life) of a therapeutic dose in healthy adults is 22 ± hours but children metabolize the drug more rapidly. For those of you who are "squeamish" the next two paragraphs may be skipped. I am not prejudiced against "squeams" and I hope I will not get letters from the Squeamo-American Society.

The *toxicokinetics* (there's that word again) of phenytoin is both fascinating and useful in terms of the clinical course and management of the overdosed patient. The T½ is dose dependent, i.e., the time required for the plasma level of this drug to halve increases as the concentration of the drug increases. In therapeutic doses, elimination of phenytoin follows what is referred to as *first-order kinetics,* i.e., the transfer of a constant fraction of a drug per unit of time. Thus the rate of transfer in first order kinetics is directly proportional to the amount of drug remaining to be processed. In such a process a drug with a T½ of 8 hours and an initial concentration of 40 μg/ml will have a concentration of 20 μg/ml 8 hours later and only 10 μg/ml 8 hours after that and so on.

In the patient acutely overdosed with phenytoin a different kinetic elimination process occurs, known as *zero-order kinetics.* In this process, elimination occurs at a *fixed* rate regardless of the amount of drug remaining instead of at a rate proportional to the concentration of drug present as in first-order kinetics. Under zero-order kinetics, with higher doses, the plasma level of phenytoin increases disproportionately. Why is this true in acute phenytoin overdose, you ask? Probably because the enzyme systems needed for elimination of this drug are saturated with larger doses and elimination is impaired. As a general rule, with drugs requiring hepatic enzymes systems for detoxification these enzymes have the potential to be saturated. The concept of enzyme saturation explains why serum levels decrease quite slowly following a large overdose, but then these same levels decrease more rapidly as the serum concentration falls. Simply stated, when a patient incurs an overdose with phenytoin, the clinical features of toxicity may persist for days until the metabolic rate of elimination increases and phenytoin levels decrease below the toxic range.

The typical clinical features of a patient acutely overdosed on phenytoin consist of the well known triad of *nystagmus, ataxia,* and *drowsiness.* Most of the adverse clinical findings are confined to the central nervous system. The earliest detectable sign of acute overdose is *nystagmus* on lateral gaze. A plasma phenytoin level taken at this time will probably be > 20 *μg/ml* (a therapeutic phenytoin level is 10-20 μg/ml). With increasing accumulation of the drug, progressive spontaneous horizontal nystagmus occurs. When the level exceeds *30 μg/ml ataxia* ensues. The most striking and fairly consistent toxic effect of phenytoin

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seems to be on cerebellar function. As the level rises > 30 μg/ml nystagmus can become vertical, speech becomes slurred and drowsiness is often present. The gross ataxia and incoordination of the trunk and limbs produce a lurching gait in the patient, with a rather characteristic coarse tremor of the extremities on voluntary movement. This incoordination frequently progresses to the degree that patients cannot walk and some cannot even stand. With even more increased dosage consciousness may be depressed to the extent that the patient is not only drowsy, but confused and disoriented often with hyperactive or manic behavior. A totally unresponsive state is really quite uncommon and respiratory depression is also unusual. If you suspect phenytoin overdose in your patient and the patient is in coma, look for another cause. The deep tendon reflexes are normal or increased and the pupils may be dilated.

It is easy to see that if you are confronted by a patient with nystagmus, ataxia, hyperactivity, and disturbances in consciousness and you don't have a history of drug overdose you might consider other diagnoses. Certainly the possibility of a posterior fossa tumor must enter your consciousness as well as acute viral cerebellitis, Guillain-Barré Syndrome, botulism, hysteria, and a host of others as they say. Choreoathetosis has been described with acute phenytoin overdose and quite closely resembles Sydenham's Chorea. It is fair to state, however, that the most common cause of acute ataxia in all age groups is overdose of intoxicating drugs or toxic compounds.

Phenytoin is an effective antiarrhythmic drug useful in controlling abnormal rhythms in overdoses due to drugs such as digitalis and tricyclic antidepressants. Phenytoin apparently stabilizes membranes and thus prevents the spread of seizure discharges in the CNS, but in the cardiovascular system this characteristic of membrane stabilization can decrease the automaticity of the SA node and increase AV block. Cardiovascular toxicity with this drug is generally limited to patients receiving rapid IV infusions or in massive oral overdose. The cardiovascular effects of phenytoin include a decreased rate, an increase in AV block, ventricular fibrillation, direct myocardial depression, decreased cardiac output leading to congestive heart failure, idioventricular rhythm, hypotension, asystole and death.

The diagnosis depends of course on a good thorough history and physical exam plus serum phenytoin levels. Because of protein binding, age, race, and a bunch of other factors, exact correlation between serum phenytoin levels and toxicity probably do not exist; however, levels < 15 μg/ml are rarely associated with toxicity and levels > 95 μg/ml have been associated with fatalities. In this poisoning the EEG shows slowing of the alpha waves but of course this is not specific for this poisoning.

The treatment of acute phenytoin overdose is fairly straightforward: (1) withdraw the medication if the patient is taking the drug on a chronic basis, (2) obtain serial serum phenytoin levels, (3) carefully monitor the patient. In an emergency room encounter with a patient involved with an acute phenytoin overdose, gastric emptying is indicated followed by administration of activated charcoal and a saline cathartic such as magnesium sulfate. In very severe overdoses involving this drug the use of hemodialysis to increase the elimination of phenytoin is probably an exercise in futility; the protein binding of phenytoin is extremely high and dialysis probably is not going to benefit the patient very much (it won't do much for the poison-treater either). Charcoal hemoperfusion may be of value in some problem overdose cases although good data are not available, in my opinion, to champion its use. Fortunately the prognosis for phenytoin overdose is really quite good without heroic measures. Most of your patients will get better with little more than gastric emptying, charcoal, a cathartic, and observation.

The cardiovascular problems resulting from acute overdose can be treated as follows: (1) Complete heart block can be overcome with intravenous atropine. (2) Effective cardiac rhythm and output have been reported improved following the administration of epinephrine. A temporary pacemaker can be used if the usual measures fail. (3) Hypotension could be remedied by correcting volume deficits and, if this fails, administering (+) inotropic agents such as dopamine.

It would be unfair to the reader to leave this subject without mentioning the peculiar phenomenon of *paradoxical intoxication*. This has been defined as the situation in which seizure frequency increases as the serum level of the phenytoin increases. In the usual case of this unusual state although the phenytoin level can be quite elevated there are few or no toxic features such as nystagmus or ataxia. You could possibly expect to see this condition in patients on chronic phenytoin therapy. The treatment for the seizures should not include giving more phenytoin but rather stopping the offending drug and administering a drug like diazepam. The diagnosis of paradoxical intoxication depends on your thinking of it and obtaining a serum phenytoin level.

Epilepsy is certainly a disease state that has been a mystery since people first became aware of differences in the behavior of their neighbors. Through several millenia the causes of this malady have given rise to many theories and treatments which we look upon today as being bizarre. What will the medical historian of the future think of our "modern" medicine? Will they think of our numerous blood tests for the diagnosis of epilepsy and monitoring for anticonvulsant levels as nothing more than blood-letting to get rid of "evil humors"? Will they view the electroencephalogram as a form of "medical" trephining? Will they think of our anticonvulsant armamentarium as chemical exorcism? I have seen neurology residents, when treating an unresponding status epilepticus, make a cross from two tongue depressors and place it in front of the convulsing patient in an effort to stop the process. I personally believe that a garlic amulet works better.

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Income Maintenance in Retirement and the Need to Rethink Family Policy

Angela M. O'Rand, Ph.D.

Background

In 1977 the dependency requirement of the Federal Old-Age, Survivars, and Disability Insurance Benefits pragram was eliminated. This pravisian was enacted, in part, as a respanse ta the Supreme Caurt Decisian in *Califana v. Galdfarb,* which faund gender-based distinctions regarding survivars benefits ta be in direct vialatian af the Due Pracess Clause af the Fifth Amendment. Lean Galdfarb, a retired federal emplayee, had been denied widawer's benefits fram his deceased wife's sacial security since he had nat been receiving at least ane-half suppart fram his wife at the time af her death. This dependency requirement far survivar's benefits did nat apply ta widaws as well.

Califana v. Galdfarb determined this denial ta have deprived Hannah Galdfarb, his deceased wife, af her entitlement ta pratect her family. Hannah Galdfarb had warked in the New Yark City public schaal system far nearly 25 years until her death in 1968 and had paid all sacial security taxes in full during her tenure. The Supreme Caurt decided that she "was entitled ta the dignity af knawing that her sacial security tax wauld cantribute ta their jaint welfare . . . and ta her husband's welfare shauld she predecease him" (Kay, 1981: p. 81).

Althaugh this case focused specifically an the issue af dependency benefits under Sacial Security, it alsa painted ta the general pattern in aur saciety to ignare the marital band as a symmetrical ecanamic partnership, in which bath partners are entitled ta share equally in their jaint earnings, savings and investments nat anly during the life af their marriage but alsa after it has been dissalved. The failure ta recagnize marriage as a symmetrical ecanamic partnership, regardless af the divisians af labar fallawed by the cauple, has discriminated against widawers in the past and cantinues ta create special prablems af ecanamic dependence far all surviving spauses and farmer (divarced) spauses wha cannat easily qualify far benefits fram either Sacial Security or private pensian plans that exclude them. Since wamen are averwhelmingly represented in these categaries, they cantinue ta be victims af a discriminatary family policy embedded in the law, in the practices af gavernmental regulatary and service agencies and in private firms. But, as *Califano v. Galdfarb* illustrates, such a family policy also discriminates ultimately against men.

Inadequacy of Current Policy

Current policy generally daes nat recagnize wamen's ecanamic cantributians ta their families, whether ar nat they participate in the paid labar farce. Hamemakers and unpaid warkers in family businesses are natable examples of family partners whase ecanamic roles are ignared. But, as was true far Hannah Galdfarb, wamen wha are or have been paid warkers are still treated as nanecanamic cantributars ta the family. Such an implicit family policy is incansistent with wamen's lives and with the needs af their families.

This article pravides a backgraund far and the praspects af changing this inequitable palicy, particularly as it applies ta the incame maintenance prablems af alder wamen taday and in the future. This averview begins with a prafile af an illustrative cahart af wamen barn in 1914 wha reached age 65 in 1979. Their experience acrass the life caurse and at retirement farms the vanguard experience far farmulating and assessing future policy decisians regarding family ecanamic rales and retirement pragrams. Then, recent prapasals supparted by the 1983 Natianal Cammissian an Sacial Security Refarm pertaining ta the cancept af "earnings sharing" are reviewed as exemplary far rethinking the family policy required far the future.

The 1914 Birth Cohort of Women in the U.S.

Wamen barn during the secand decade af this century experienced the depressian as young wamen,

From the Department of Sociology, Duke University, Durham 27710. Reprinted from *Advances in Research,* a publicatian af the Duke University Center far the Study of Aging and Humon Development. Illustrotions by Ernest Croige, M.D.

World War II as young workers, and the fifties as mothers of the leading edge of the baby-boom generation. Their lifetime experience as a cohort was shaped by the major parameters that still define the lives of many women today. Increasing labor force participation, a higher divorce rate and the persistent earnings gap between the sexes have characterized their lives. The figures in table 1 profile their lives in these areas. Women born around 1914 are followed in five-years intervals, starting in 1950 when they approached midlife.

Overall, women in this cohort have led heterogeneous work and family lives. Since 1950, at least half of the women in this cohort have been out of the labor force at any given time. The mid-1960s mark the period of the highest labor force participation of this group, about 49 percent. The median earnings level achieved by these women has never exceeded half of men's median earnings in the same age group. In the 1970s, women in this group came closest to their male counterparts' earnings level, about 49 percent.

Two types of factors account in large part for these labor force and earnings patterns: family role demands and restricted occupational and industrial opportunities. Research on the life histories of women in this cohort shows that they have tended to interrupt or to delay their work careers in response to childbearing and childrearing roles. These role schedules at home, at work, or both have slowed their progress, as a group, in earnings achievement and in pension eligibility. However, even when women's role schedules are taken into account, the kinds of occupations and industries in which they are able to find jobs are characteristically low wage and limited in career opportunities. Four out of five clerical workers and nearly two-thirds of service workers are women. In 1970, when the 1914 cohort of women were in their midfifties, over half of those in the labor force at that time were located in either low-level clerical or service jobs.

The notable third pattern in these women's adult lives that can be observed in table 1 is their cohort experience of increased divorce over time. Younger cohorts of women have experienced much higher rates of divorce; but the 1914 cohort of women have also participated in the long-term secular trend of increasing divorce rates. In the 1950s about 4 percent of those ever-married in this group were divorced; by the 1970s, when the most spectacular increases in divorce rates in the United States were witnessed, this cohort's rate had also increased to about 6 percent. These figures, of course, underestimate the rate of those ever-divorced in this cohort, which has been determined to be about 16 percent.

Two to three million women were estimated to fall into the category of "displaced homemakers" by the end of the 1970s. Most of these women were over the age of 50 and had pursued lifestyles to that point which had assumed that their marriages would provide their lifetime needs in retirement, health and social support. Accordingly, they had invested their lives as unpaid workers at home until, for many, widowhood, separation or divorce changed their circumstances.

The Outcomes of Three Problems

These three patterns — labor force participation, earnings history and divorce rate — take on a special importance for retirement income. Lower levels of labor participation and earnings work against individual retirement savings. This occurs because retirement benefits are (1) tied to minimum tenure requirements for vesting and eligibility, (2) calculated on the basis of preretirement earnings levels, and (3) unavailable to large segments of workers (particularly women and blacks) in industries characterized by very poor pension opportunities. The results are that women are half as likely as men to be covered by private or government

Table 1

Labor Force, Earnings and Divorce Histories of Women Aged 65 in 1979 For Period Between 1950 and 1979

Years of Observation of 1914 Birth Cohort (Aged 65 in 1979)		Percent of Cohort in Labor force[a]	Annual Earnings[b] Median Earnings ($)	As Percent of Men's Earnings in Same Cohort	Percent of Divorced to those Ever Married[a]
	(approximate age)				
1950	(36)	34.0	1297	41.8	3.9
1955	(41)	40.5	1706	41.0	
1960	(46)	47.4	2205	44.5	4.6
1965	(51)	49.4	2715	45.8	
1970	(56)	47.4	3747	48.8	5.4
1975	(61)	34.5	5020	48.2	
1978	(64)	33.6	5108	46.2	6.4
1979	(65+)	8.3	——	——	3.9

[a] Labor force rates and divorce rates drawn from Tables C.4 and C.7 and B.6, respectively, in George Masnick and Mary Jo Bane's *The Nation's Families: 1960-1990*, Joint Center for Urban Studies of MIT and Harvard University, Cambridge (1980), pp. 174, 183 and 153.

[b] Earnings data based on estimated averages for cohorts born between 1911 and 1915 reported in Table 36, *Annual Statistical Supplement, 1981, Social Security Bulletin*, 45 (November 1982) p. 90.

pensions ot retirement ond thot Social Security benefits based on their own eornings records ore often lower than 50% of their spouses' benefits.

The chief odvontoges for women of the Sociol Security system ore thot the system is neorly universally ovailable (more thon 90 percent of the poid lobor force is covered by the system) and redistributive feotures of the system fovor low-woge workers in benefit returns (although the regressive woge tax during the working years hits the lower woge worker horder). In the privote sector, however, pension plons vary widely in their "benefit promise," that is, in the extent to which workers can successfully quolify for finol benefits ond in the level of benefits thot con be achieved. Workers in the finonciol, communicotion, tronsportotion, utilities, insurance, real estote, ond selected monufocturing (usuolly unionized) industries hove greoter benefit promise, while those locoted in construction, wholesole ond retoil trade ond service (especiolly personol service) sectors hove much less benefit promise. Women ond nonwhites are overrepresented in the lotter sectors.

Furthermore, if o retired womon is widowed or divorced, she moy lose eligibility for her former spouse's retirement benefits from oll sources. Few privote pension progroms provide survivors' benefits; when they do they require the primory retiree to hove met eligibility requirements fully, to hove stoyed morried to the survivor, not to have died too soon, ond/or to hove reduced his/her own benefit os a provision for the survivor(s). This lost provision usuolly is presented os o "joint/survivor option" to the worker; thus automotic postretirement survivors' benefits ore not widely ovoiloble. Under Social Security o divorced womon con quolify for a 50 percent dependent benefit from her former spouse's occount only if the morrioge lasted ot leost 10 yeors ond only when the former spouse himself retires. Under privote pension plans, divorced persons hove no protection ot all.

The prevolence of poverty omong older women expresses one outcome of women's disadvontoged benefit stotus. By the lote 1970s, two out of three persons oged 65 or more who fell below the poverty line were women. About one out of three nonmorried (widowed, divorced, separoted) women over 65 fell below the poverty threshold. And, of oll oged persons receiving Supplementol Security Income (SSI), the progrom established in 1972 to ossure o minimum income to the eligible oged or disobled person living in his/her own household, three out of four are women.



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The median earnings level achieved by these women has never exceeded half of men's median earnings.

Thus, the life course experiences of women reoching old age in 1979 point to limited opportunities for individuol retirement soving omong women ond to on implicit fomily policy underlying retirement progroms thot ignores women's economic contributions to the fomily. This leoves the older, unmarried (widowed or divorced) womon in triple jeopardy with respect to poverty. Her family role hos limited exchange volue during morriage ond even less after the marrioge hos ended.

Toward a New Policy: Earnings Sharing for Income Maintenance

Since its introduction in 1976 by House Representatives Mortho Keys and Don Froser, the concept of eornings shoring hos goined increosing support os the best solution of problems of retirement coverage of men and women olike. The 1983 report of the Notionol Commission on Sociol Security Reform reiteroted the recommendotions of the 1979 Advisory Council on Sociol Security ond the 1980 President's Commission on Pension Policy by noting the following:

> . . . Earnings shoring is o recognition of marrioge os on economic portnership with equol respect given to the division of lobor chosen by eoch couple. It occords the right to each individuol to o retirement income bosed on holf of the total retirement credits eorned by the couple during their morrioge. This is similor in concept to the shoring of income in the joint tox return of o morried couple. Working women would hove o continuous record of Sociol Security credits when they retire insteod of zero credits for yeors spent in the home. It would respond to, and recognize, the economic value to the couple of full-time work in the home by either spouse. (1983: pp. 16-17).

In oddition to protecting the homemaker, eornings sharing also provides the simple formulo wherein either spouse benefits from the retirement credits of the couple as o unit. Thus, o wife working under Sociol Security and a husband not covered by Sociol Security in his employment



Workers in retail trade and service (especially personal service) sectors have much less benefit promise.

(remember Leon Goldforb) both receive credit from her coveroge. The extension of the earnings shoring cancept to privote ond public pensian systems would follaw the some principle. Should the morrioge be dissolved far any reoson, the investments by both spauses during the period of their union continue to be recagnized officiolly far earnings credit ond survivor benefits purpases.

Toble 2 summarizes selected feotures of the provisions for retirement benefits under the present law and under on earnings shoring praposol. The toble's contents ore drawn from heorings before the Task Force on Sociol Security and Women of the Subcommittee on Retirement Income ond Employment ond the Select Committee on Aging of the House of Representotives on the Treotment of Wamen Under Social Security, conducted between May 16 ond August 13, 1979. The earnings sharing option praposes to redefine the economic division of labor of marrioge by treating both portners as economic contributars to the fomily unit, by eliminating the concept of "dependency," and by not penalizing single workers or higher eorners before or after marrioge.

Eornings credit and eligibility for retirement benefits from Sociol Security ore provided to the couple for the period of their morrioge during which ot leost one af them hos covered emplayment. Individual earnings records wauld be maintoined for cauples ta protect individuals fram income loss due to inevitoble morital dissalution. Surviving spouses thus can benefit cantinuously from the stondord of living achieved by the cauple. The oged hamemoker is not treoted as a dependent, but as o retired partner of the retired warker; the division of labor odopted by this couple is not penalized. Finolly, the divorced person is pratected as well.

Prospects for the Future

Trends in labor participation, morrioge and divorce observed in different coharts af women in this century accentuate the problemotic feotures of the 1914 cohort's experience. Older women in the future will opprooch their 65th birthdays in larger numbers with higher rotes of work and divarce. The some is true, of course, of older men in the future. Public ond privote policies towards the fomily can serve to exocerbote or to omeliorate the problems of the future elderly.

While earnings shoring does not resolve oll the problems of higher dependency ratios, sex discriminotion, voriable pension systems ocross industrial sectors, ond poverty omang the elderly, it does odopt o definitian of morrioge os o partnership ond thereby anticipotes o structurol problem in income maintenance among the elderly. Eornings shoring adjusts for the voriability in the family ond work lives of both men and women without penalizing segments of the elderly population far chaasing o porticulor lifestyle. Finally, it simultaneously protects the individual worker ond homemaker from precipitous income loss os o result of a chonge in morital status. As such, earnings shoring represents a useful redefinition of the fomily for public policy purposes.

Table 2
Comparison of Major Provisions Under Present Law and Earnings Sharing Option[a]

Provision	Present Law	Earnings Sharing
Eligibility for retirement benefits	Person must have worked in covered job long enough to be insured for benefits or be a dependent of such a person.	At least one spouse must be insured as under present law.
Earnings credit	Person gets earnings credits based only on his/her own work in covered employment.	Total earnings of married couple divided equally between them for each year of the marriage and credited to their individual earnings records. Surviving spouse credited with 80% of earnings credits of couple (or 100% of higher earner's credits).
Benefits		
A. Retired worker (married, separated or divorced)	Gets weighted benefit based on own earnings credits.	Gets weighted benefit based on half of couple's earnings credits while married and own earnings credits while single, plus any credits acquired as a result of a prior marriage.
B. Aged homemaker (married, separated or divorced)	Dependent spouse's benefit equal to 50% of retired worker's benefit.	No dependent spouse's benefits; gets benefits based on any earnings credits acquired through work or marriage.
C. Aged widow(er)	Dependent's benefit equal to 100% of deceased worker's benefit.	No dependent surviving spouse's benefit; gets benefit based on earnings record as described above (including credits inherited when spouse dies).

[a] This table is drawn from the U.S. House of Representatives, Hearings on the *Treatment of Women Under Social Security*, Select Committee on Aging, Washington, D.C., Government Printing Office (1980), Table 3, pp. 137-138. The source table described another option and includes provision information on children, mother's and father's benefits, young widows and disabled persons.

Postscript

This essay has not addressed the very important (and related) issue of health maintenance in retirement. As in the case of income maintenance, lifetime patterns of living and structurally mediated opportunities for promoting health and for coping with acute disease episodes and chronic illness influence status in later life. For women, who live longer but not necessarily healthier lives than men on the average, the prospects for successfully coping with age-related disease patterns (e.g., osteoporosis, diabetes, and cancer) are related to their economic and marital circumstances. Much more research is needed on the variable and predictable features of these problems.

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Breast Feeding and Cold Medications

Steve Saxe, R.Ph.

The common cold, olso known as acute rhinitis, infectious rhinitis, grippe, catarrh or coryzo, is coused by ane or more invading viruses. The symptoms usuolly lost 7-10 doys. Patients frequently complain of feverishness (but seldom fever), generolized discomfort, runny nose, sore throot, headache, cough or congestion. Becouse o cold is caused by viruses there is no "cure." The cold medicatians that have been morketed ore designed to decreose the severity af these cold symptoms.[1, 2]

For most people the selectian of a cold preporotion is relotively eosy. For wamen who ore breast feeding, however, the choice is not so simple. Many medicotions are found in breost milk in sufficient quantities to offect the infant. Since the common cold has no cure, ovaiding all cald medicotions is the best plon when breost feeding. Vorious nondrug treatments may help relieve some of the cold symptoms. Use of a humidifier and drinking plenty of fluids will help nosol stuffiness ond chest congestion. Moist heat packs to the face may help relieve painful sinuses. Sucking on hard condy moy relieve o sare throot. Also, eoting well ond getting plenty of rest will help the body fight the cold ond produce enough milk.[1, 2]

From the Department af Pharmacy Services, Moses Cane Memarial Haspital, Greensbara 27401-1020.

If a cold medicotion must be used, the ingredients should be corefully checked. Long-octing preporations should be avaided ond the smollest effective dose should be taken. The medicotion should be token right ofter nursing, ond o close watch an the infant ond the supply of milk should be mode for any signs of odverse effects. The infont moy shaw signs of irritobility, sleep disturbonces, excessive drowsiness, tremors or subtle changes in behavior, while the mother's supply of milk may decreose. Most importont is to remember that medicotions will not cure the cold, only moke it mare talerable.

The common ingredients found in cold preparotions include antihistamines, decongestonts, expectoronts, cough suppressonts, poin ond fever medicotions. Unfortunotely, the interest in studying the eliminotion of these drugs in breost milk is foirly recent and good informatian is lacking. This article will present the availoble dato to help the nursing womon make on informed decision.

Histomine is released as o result of the reoction between the body's defense system ond o foreign substance. This type of reoction is usually seen with pollen-induced ollergic rhinitis. Allergic rhinitis is often treoted with ontihistomines which block the histamine-induced runny nose. The runny nose of a cold is nat felt to be caused by histamine. However, one of the effects of ontihistamines is the obility to dry up mucous secretions which may relieve the runny nose.[1]

Chlorpheniramine, brompheniromine ond diphenhydromine ore the antihistomines usually used for ollergies or cold symptoms. In generol, antihistamines are not found in lorge enough quontities in breost milk to affect the infant. Because of their obility to decreose various secretions, antihistomines could decrease or stop the supply of breost milk. There is no documentation to support this inhibition, but it is o risk thot must be considered.[3, 4]

Decongestonts ore the most common ingredients in cold medicotions. They work by constricting blood vessels which, in turn, couse a shrinkage

COMMON COLD MEDICATIONS

Product	Dosage	Decongestant	Antihistamine	Pain and Fever	Other
1. Alka-Seltzer Plus	Effervescent tablet	Phenylpropanalamine 24.08 mg	Chlarpheniramine 2.0 mg	Aspirin 324 mg	
2. Chlartrimetan	Tablet		Chlarpheniramine 4 mg		
3. Cantac	Time capsule	Phenylprapanalamine 50 mg	Chlarpheniramine 4 mg		
4. Caricidin	Tablet		Chlarpheniramine 2 mg	Aspirin 325 mg	
5. Ca-Tylenal	Tablet	Pseudaephedrine 30 mg	Chlarpheniramine 2 mg	Acetaminaphen 325 mg	Dextrametharphan 15 mg
6. Dristan	Time capsule	Phenylephrine 20 mg	Chlarpheniramine 4 mg		
7. Sinutab	Tablet	Phenylprapanalamine 25 mg	Phenyltalaxamine 22 mg	Acetaminaphen 325 mg	
8. Sudafed	Tablet	Pseudaephedrine 30 mg			
9. Sudafed Plus	Tablet	Pseudaephedrine 60 mg	Chlarpheniramine 4 mg		
10. 4-Way Cald	Tablet	Phenylephrine 12.5 mg	Chlarpheniramine 2 mg	Aspirin 324 mg	

COMMON NASAL SPRAYS

Product	Form	Decongestant	Other
1. Afrin	Nosol sproy	Oxymetozoline 0.05%	
	Nose drops		
2. Alconefrin	Nose drops	Phenylephrine	
3. Coricidin	Nosol sproy	Phenylephrine 0.5%	
4. Driston	Nasal sproy	Phenylephrine 0.5%	Pheniromine 0.2%
5. Durotion	Nasal sproy		
	Nose drops	Oxymetazoline 0.05%	
6. Neo-Synephrine	Nosol sproy	Phenylephrine (spray — 0.25	
	Nose drops	ond 0.5%) (drops — 0.125, 0.25, 0.5 and 1%)	
7. NTZ	Nosol spray		
	Nose drops	Phenylephrine 0.5%	Thenyldiomine 0.1%
8. Privine	Nosal sproy		
	Nase drops	Naphozoline 0.05%	
9. Sinutab	Nosol sproy	Xylometozoline 0.1%	
10. 4-Woy	Nasal sproy	Phenylephrine 0.05% Naphozoline 0.05%	Pyrilomine 0.2%

of swollen mucous membrones. This decreoses nosol stuffiness ond improves sinus droinoge. Decongestonts ore odministered either orolly or topicolly os nasal sproys or drops. The orol decongestonts include ephedrine, pseudoephedrine, phenylephrine and phenylproponolomine. Decongestonts used in nosal sproys or drops include phenylephrine, nophozoline, oxymetozoline ond xylometazoline.

There is little informotion ovoilooble discussing the effects of decongestonts on on infont when used by o breost-feeding womon. One cose hos been documented of on odverse effect from pseudoephedrine. A three-month-old infont exhibited signs of irritability, excessive crying and disturbed sleep ofter the child's mother hod token o sustoined-oction pseudoephedrine product for 1-2 doys. The symptoms resolved 12 hours ofter she discontinued the medicotion. It is hord to soy if the symptoms resulted from the use of a long-acting product or if pseudoephedrine would couse the effect regordless of dosoge form.

Phenylephrine is thought to be sofe either orolly or os o nosol sproy. When taken orolly, o lorge omount of drug is destroyed in the stomoch without being obsorbed. Any phenylephrine obsorbed into the body either orolly or nosolly is broken down or metobolized quickly. Therefore, phenylephrine is believed to be of minimol risk.[3]

There is no informotion avoilable regarding the other decongestont medicotions. The sofest one oppeors to be phenylephrine, but most orol forms are combined with ontihistomines. Nosol sproys contoining only phenylephrine ore ovailoble (Neo-Synephrine, Coricidin ond others) ond these moy be the sofest form of decongestont theropy.

Cough is often on irritoting symptom of the cold. Coughs are usuolly clossified os productive, one removing occumuloted phlegm from the respirotory troct, or nonproductive, o dry noncongested cough.

A productive cough is treoted with expectorants which ore formuloted to decreose sputum viscosity. This eases the expectoration or removol of the phlegm from the respirotory troct by the cough. Expectorants ore believed to work by stimuloting secretions of respirotory troct mucous glonds which decreose the viscosity of occumulated phlegm. This is be-

COMMON COUGH MEDICATIONS

Product	Cough Suppressant	Expectorant	Other
1. Benylin	diphenhydromine 2.5 mg/ml		olcohol 5%
2. Cherocol	codeine 2 mg/ml	quoifenesin 20 mg/ml	olcohol 3%
3. Cheracol D	dextromethorphan 2 mg/ml	quoifenesin 20 mg/ml	olcohol 3%
4. 2/G		quoifenesin 20 mg/ml	alcohol 3.5%
5. 2/G-DM	dextromethorphan 3 mg/ml	quoifenesin 20 mg/ml	olcohol 5%
6. Novahistine Cough ond Cold	dextromethorphon 2 mg/ml		pseudoephedrine 6 mg/ml chlorpheniromine 0.4 mg/ml alcohol 5%
7. Novohistine Expectoront	codeine 2 mg/ml	quaifenesin 20 mg/ml	phenylproponolomine 3.75 mg chlorpheniramine 0.4 mg/ml alcohol 7.5%
8. Robitussin		quaifenesin 20 mg/ml	alcohol 3.5%
9. Robitussin AC	codeine 2 mg/ml	quaifenesin 20 mg/ml	olcohol 3.5%
10. Robitussin DM	dextrometharphan 3 mg/ml	quaifenesin 20 mg/ml	olcohol 1.4%

lieved to result from a direct stimulus ta the glands ar o reflex reactian from irritoting the gastraintestinal tract.

There is little evidence ovoiloble supparting the efficacy of expectorants, but they continue to be widely used. Guaifenesin is on expectarant excreted in the breost milk in small quantities with na effect expected on the infant. Mast ather expectaronts potentially hove o deleterious effect on the infont ond their use is not recommended.

A nanpraductive caugh is annoying to the potient os well as irritating to the throat. Since this irritation perpetuates the caugh, a patient shauld try a cough suppressant. The two most popular cough suppressants are dextrametharphon and codeine. These drugs work by depressing the cough center which triggers the cough.

Na information is ovoilable regarding dextramethorphan excretion in breost milk. Though it is not expected ta cause a problem if used in judicious doses, a definite onswer cannot be given at this time. Normal dases of cadeine are excreted in breast milk, but in quantities insufficient to affect the infont.[3-5]

Heodache ond a feeling of feverishness (thaugh seldam actual fever) are frequent complaints of the common cold. Both symptoms are effectively treated with aspirin or ocetaminaphen (Tylenol, Datril ond others). Small quantities of ospirin are excreted in breast milk, and there is o slight possibility that ospirin could increase bruising or bleeding tendencies in the infont. An occosionol dase of aspirin taken ofter breast feeding is felt to be sofe with o healthy infant. Acetaminophen in normal doses is olso felt to be safe, when the breast feeding infont is healthy and has normol liver functions.[4, 5]

Unfartunately, when discussing cold medicotions ond the breastfeeding mother, there are no simple answers. Eoch person must look ot the available informatian, and weigh the possible side effects ond risks to the infant ogoinst the benefits sought from treatment. Above all, consult with a physician or pharmacist befare toking any medicotion when breost feeding.

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AIDS and Blood Transfusions

Whot follows is o joint stotement on directed donotions of blood, o new proctice thot hos evolved os o result of feors of controcting AIDS from blood tronsfusions. The stotement comes from the Americon Red Cross, the Americon Associotion of Blood Banks, ond the Council of Community Blood Centers.

The current epidemic of ocquired immune deficiency syndrome (AIDS) ond attendont publicity hove led to concerns thot AIDS moy be tronsmitted by blood tronsfusion to persons not in one of the recognized high risk groups. Of 1,601 coses of AIDS reported to the CDC, 94 percent hove occurred in people belonging to four groups: homosexuol or bisexual moles with multiple sex portners; introvenous drug abusers, recent entronts from Hoiti, ond persons with hemophilio. Only one newborn infont ond 14 odult recipients of blood tronsfusions have been identified os coses of possible tronsfusion-ossocioted AIDS. More thon 10 million persons were tronsfused in the United Stotes during the three-yeor period that these coses were reported ond, therefore, it oppeors ot this time thot the risk of possible transfusion-ossocioted AIDS is on the order of one cose per million potients transfused.

On Morch 25, 1983, in response to the potentiol risk of transfusion-ossocioted AIDS, we pledged complionce with the Recommendotions on AIDS by the Office of Biologics, FDA, and jointly implemented a notionwide progrom to inform all blood donors of AIDS risk groups and provided means for individuols in high risk groups to be excluded os blood donors. We concur with Secretory of Heolth ond Humon Services Morgoret M. Heckler's stotement of June 14, 1983, that ". . . all of us might olso be confronted with on unnecessory ond unjustified level of feor, if misunderstonding of AIDS is ollowed to grow. Such o level of fear could octuolly impede us in our real tasks. . . ."

One consequence of the understondable, but excessive, concern for transfusion-ossocioted AIDS hos been requests by potients ond their physicions to hove blood donors selected from fomily members, friends, coworkers, ond even newly formed privote donor clubs. There is no evidence to support this notion thot these "directed donotions" ore safer thon those available through the community blood bonk.

The concept thot fomily members, friends, coworkers, church members or other selected groups are sure to provide sofer blood is unreolistic. These some individuols are ond hove been the notion's volunteer blood donors who hove, in the post, given freely for oll patients rother than for o porticulor individuol. There is no reoson to think thot segregoting these individuols into selected donor ponels will provide safety over ond obove the level provided by current orrangements. In addition, a system of directed donotion moy creote intense pressures on fomily ond friends who moy therefore be untruthful obout their obility to meet donor requirements. It is possible thot the administrative ond operationol complexity that will be port of ony widespread opplication of directed donotions moy lead to o significont increase in clericol errors ond, in this way, reduce the sofety of tronsfusion.

Finolly, there is the risk thot widespreod attempts to direct donotions, while not increasing the sofety of tronsfusions, will seriously disrupt the notion's blood donor system. Voluntory donotion is essentiol for meeting our notion's needs for blood and blood products. There is o real concern thot donors moy refroin from routine blood donotions while owoiting requests to provide directed donotions ond, thereby, could disrupt the blood supply to the point thot routine ond even some emergency needs for transfusions moy go unmet.

Given these considerotions, we strongly recommend thot "directed donotion" progroms not be conducted. We reoffirm our commitment to o sofe blood supply for oll recipients, to mointoining the highest stondords possible for selecting volunteer donors, ond to strict complionce with pertinent recommendotions by the United States Public Health Service ond other federol regulotory bodies.

The Americon Red Cross Carolinas Region has issued the following informotion obout AIDS ond blood tronsfusions in North ond South Corolino.

The oppearance ond increose of coses of Acquired Immune Deficiency Syndrome (AIDS) hove impressed people ond oll types of medio, creoting on otmosphere of fear.

There were 2259 reported coses of AIDS as of September 2, 1983. Over 71% of the cases occur in mole homosexuols with o greot mojority in New York ond Son Froncisco. Introvenous drug users who shore needles ore the second populotion involved, and heterosexual Hoitians represent the third group. Tronsmission seems to be NOT CASUAL but by intimote sexuol contoct.

Blood related coses ore suspected in intravenous drug users; obout 1% of the coses ore hemophiliacs who used lyophilized ontihemophilic foctor concentrates (populotion pool up to 20,000 donors) ond in lesser degree cryoprecipitote (one donor per

bog used — opproximotely 100 units). There is only ane blood reloted exomple in o premoture boby in Son Froncisco, Colifornio, who wos tronsfused with plotelets from o donor who loter developed ond died of AIDS. Red blood cells of the some donor were tronsfused to o potient with terminal leukemio who olso died *shortly* without developing AIDS. Incubotion time of AIDS seems ta be long (up to 20 or more months). The boby mentioned above olso died apparently with AIDS suspected symptoms. About 12 million units of blood are transfused per yeor in U.S.A. The possibilities ore 1 in a million in the so-colled "Tronsfusion Reloted" coses.

The Office of Biologics of the FDA hos specificolly recommended meosures to blood collection agencies to screen ond prevent the possibility of recruiting the so-colled "high risk groups" omong blood donors. The Red Cross follows those recommendations very strictly. We believe that our blood/blood products ore safe ond follow oll requirements of the OoB.

There have been 12 cases of AIDS reported in North Carolino ond South Carolinc. Seven were homosexuals coming from New York. Six hove died. Five coses were out-of-stote residents treoted in North Corolino. Figures ore not very precise yet.

No screening tests ore ovoilable. Worning symptams include severe night sweats, unexplained fevers, unexpected weight loss, swollen glonds, or Koposi's Sarcoma (a rore concer).

The fear of ocquiring AIDS through blood/blood products may couse praspective elective surgery potients to request predonotions of their own blood for loter tronsfusions ond/or to consider directed donations (recruiting of blood donors among fomily ar known volunteers). Currently our position is os follows.

Autologaus Tronsfusions: The Regianal Director of the Blood Services in cansultation with the Regional Medical Advisory Committee hos ogreed to porticipate in on outologous tronsfusion program. Four groups of potients ore outomoticolly accepted: patients whose very rore blood types ore not ovoiloble in the inventory of the ARC Rare Donor Registry; potients in whom compotible red blood cells connot be obtained due to ontibody problems; potients whose religious beliefs do not permit blood tronsfusions from others; very specific prevention of immunizotion (tronsplonts).

The Regionol Medicol Advisory Committee recommends thot elective surgery potients for plostic surgery ond orthopedic potients os well os other speciol cases be occepted on a one-to-one bosis until the mognitude of the demond overposses actuol medico-technical possibilities.

The Medicol Advisory Committee will continue to monitor the situotion. In the event that the demond for outologous tronsfusions begins to odversely offect the region's copobilities, new regulotions would be considered.

Directed Donotions: Concern for transfusion-associoted AIDS has led to requests by patients ond/or their physicions to hove family members ond other selected individuols provide blood donotions designated for specific recipients. The Americon Red Cross, together with the Americon Associotion of Blood Bonks ond the Council far Community Blood Centers, strongly recommends thot such directed donotion progroms *not* be canducted becouse: there is no evidence to support the notion thot these donotions ore sofer than voluntory blood danations presently ovoiloble; directed donotions creote pressures on fomily ond friends who moy be untruthful in providing heolth histories in order to mointoin confidentiolity of personal informotion; widespreod ottempts to direct donotions could seriously disrupt the notion's blood supply, as needed donors refrain from giving while owoiting requests to donote for fomily ond friends.

Specific Donations: In certoin other situations, fomily members or unrelated individuols moy be selected on o scientific basis to donote for o specific recipient. To clorify why these "donor-specific" motches ore not regorded to be "donor directed" the following definitions ore provided:

> *Donor-specific Blood Tronsfusions.* Blood donotions moy be recruited from o designoted living kidney donor, usually o sibling or other relotive, for tronsfusion to the intended tronsplont recipient. Such tronsfusions benefit the recipient by improving tronsplont survivol.
>
> *Phenotype-Motched Transfusions:* Red blood cell, plotelet or gronulocyte donors moy be selected by phenotype from family members or unreloted donors for tronsfusions to olloimmunized recipients. Such immunologic motching benefits recipients by improving the effectiveness of tronsfusions.

Our medical stoff, Director, and Associote Directors will be pleosed to onswer any questions thot you hove. Our telephone number is 704-376-1661. There is olwoys 24 hour medicol coverage. The night number is 704-376-1669.

Raynaud's Syndrome

Claude S. Burton, M.D., Peter W. Heald, M.D., and J. Lamar Callaway, M.D.

Cold weother induces mony chonges in our bodies in on ottempt to conserve energy. Some of these protective reflexes ore exoggeroted in on unfortunote few, producing o drostic reduction in blood flow to the honds ond, in some coses, the feet. Rorely, ports of the foce (nose, ears, chin, cheeks) ore offected. This phenomenon hos been with us for centuries but was described in the 1800's by Dr. Roynoud ond therefore corries his nome. The dromotic chonge in the color of the skin (white to purple when blood flow is inodequote, red during the increosed flow of the recovery phose) ond the obility to reproduce the phenomenon with cold and other stimuli (emotion, vibrotion) makes the condition highly recognizoble. Roynoud's phenomenon commonly occurs olone but moy be ossocioted with serious underlying diseose. A coreful physicol exominotion ond skilled review of systems (osking questions of the potient in order to screen for molfunction of ony body system) is recommended for oll potients with this disorder to rule out other diognoses. The monogement of Roynoud's syndrome embroces mony modolities including locol, systemic, physicol, and psychiotric theropies. Skillfully blending these options with the potient's individuol chorocteristics involves the ort of medicine.

The first stoge in managing Roynoud's syndrome is to remove or control foctors thot con produce or oggrovote the condition. Repetitive trouma to the honds such os typing or jockhommer work is one stimulus thot must be controlled. Smoking must be curtoiled to improve circulotion. Medicotions such os birth control pills, propronolol, ond bleomycin can exacerbote Roynoud's syndrome and need to be reploced if possible. Since oll Raynaud's syndrome sufferers get worse with cold exposure, this olso needs to be minimized. Gloves should be kept neor the refrigerotor to be used for removing cold items. Pocket wormers ond electric socks ore inexpensive oids for the potient who ventures out of doors. Some potients hove found it useful to swing the orms about in a windmill-like pattern to force blood out into the honds. This is porticulorly helpful when an attock of Roynoud's syndrome is beginning.

If odditionol theropy is needed, there ore topicol and systemic medicotions which act on vorious components of the circulotory system to improve blood flow. The eosiest to use ore the topicol nitroglycerin ointments developed for patients with ongino. These con be opplied topicolly to the offected oreos to induce blood vessel dilotion ond thereby increose blood flow. As in ongino there is o systemic effect ond doses identicol to ongino theropy are utilized. Systemic blood vessel diloting ogents hove o long history in the monogement of the Roynaud's syndrome. If the potient hos high blood pressure these ore useful; otherwise the side effects of lowered blood pressure ond fluid retention (often requiring diuretics) ore disconcerting. Medicotions utilized include nifedipine guonethidine, reserpine, methyldopo, prozosin, terbutoline, ond phenoxybenzamine. Introorterial reserpine injection may be useful in monoging on ocute ottock os it reliably produces locol vasodilotion ond wormth.

Another opprooch is to decreose the stickiness of the blood. This can be occomplished by inhibitors of plotelet oggregotion: ospirin, persontine, ond introvenous dextran. Since elevoted fibrinogen levels con cause the blood to sludge, there ore treotments designed to lower the level of this protein in the blood. Vorious mole hormones will accomplish the same thing but with side effects thot include faciol hoir growth, deepening voice, ond fluid retention. Some physicions use cobro snoke venom (Ancrod) to deplete the excessive fibrinogen. The proctice of medicine tokes on shodes of the old snoke-oil vendors with this form of treotment.

The outonomic nervous system controls the muscle tone in the blood vessels of the honds. There ore two approoches other thon medicotion thot toke odvantoge of this knowledge. The simplest of these is biofeedback. With proper troining potients con use programmed reloxotion to increase the temperoture ond blood flow of their honds. Unless there is consideroble motivotion this progrom will foil. A second opprooch is surgicol destruction of the nerves running down to the blood vessels of the extremities. This can be done on o triol bosis with the injection of o long octing, nerve blocking drug. If the trial is successful, surgery can be offered with similor results.

By reviewing the plethora of methods ovoiloble for Roynoud's syndrome the clinicion con blend the unique features of eoch potient with those of the treotments ond develop o successful theropeutic progrom.



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EDITORIAL

The Sarcoid Granuloma as an Immune Endocrine Organ

Nortin M. Hadler, M.D.

NO organism has a risk-free niche. Barriers such as skin, the mucociliary mechanisms of the airway, even tears provide some protection from external insults. Since early in phylogeny, and perhaps prerequisite to evolution, complex organisms have evolved mechanisms to compensate for the imperfections in the function of every barrier. These compensatory mechanisms are the immune system. Should an insult breach the barrier, the immune system can recognize the event, neutralize its toxicity and dispose of the insult.

In the simplest form of host defense mechanism, a foreign material breaches the host barrier defense and comes to reside in the extracellular space (where most immune responses occur). Also present in the extracellular space is a heterogeneous population of motile phagocytic cells, the macrophages. By virtue of size or charge or shape or ability to order proteins in the extracellular space, the material is recognized as foreign by a macrophage walking over its surface. That interaction leads to phagocytosis, followed by digestion and disposal.

We have evolved mechanisms that elaborate on this basic scheme, rendering it more sensitive and efficient. We can recognize a substance even if it lacks the inherent physicochemical structure to directly provoke phagocytosis. Each of us has inherited a library of stereochemical conformations or shapes that we are to recognize as foreign. This genetic library is represented in the extracellular space by a population of antibody molecules bearing binding sites, each specific for a particular shape. Should the material breaching the barrier defenses display such a shape, the resident antibody will bind it. That is a recognition event and by itself never leads to disposal. However, a series of these specific antibodies binding the particular shapes on the foreign materials creates a new surface, i.e., a display of ordered Fc regions. The motile macrophages have receptors for such ordered Fc regions and interaction leads to phagocytosis of the antibodies and the material to which they are bound. These ordered Fc coats also have the potential to activate a number of the inflammatory mediator sequences available in the extracellular space such as the complement pathways, the clotting pathway and kinins. Activation releases small peptide fragments with such biological activities as ordering phagocyte motion (chemotaxis), increasing vascular permeability, etc. The inflammatory mediators amplify the basic immune sequence by making it more likely that the motile macrophage will encounter the Fc-coated material and dispose of it.

This system has yet another mantle of sophistication illustrated in figure 1. The quantity and nature of antibody molecules present in the extra-cellular space can be varied so that when a particular shape on a foreign substance, X, is recognized, further appropriate antibodies can be synthe-

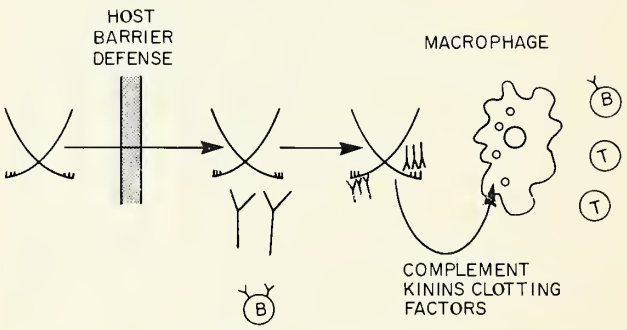


Figure 1. *Illustration of the basic element of immune defense. Assume a foreign material, X, breaches the host barrier defense. If X has a particular surface structure in the extracellular space, it will be phagocytized when encountered by happenstance by a motile or resident macrophage. In this figure, the capacity of the immune system to recognize an X with a more subtle structure is depicted. This X displays a structural configuration (antigenic shape) that the host is genetically prepared to recognize. The genetic potential is manifest in the extracellular space by antibody molecules (illustrated as Y) with binding sites specific for the shapes on X. By virtue of specifically binding to X, the surface of X becomes an ordered display of antibody tails (Fc portions). The macrophage has receptors for such an array and phagocytosis ensues. Furthermore this ordered Fc surface can activate complement, coagulation pathways and kinins creating an inflammatory milieu which enhances the efficiency of the disposal of X.*

The immune system also has the capacity to process the signal that an X is present and respond with up- or down-regulation. This is accomplished by the formation of a specific immune organ in situ. *The macrophage not only disposes of X, but translates the disposal event into a specific communication. (We don't know how, but it can!) B lymphocytes and T lymphocytes aggregate because they have specific receptors for the antigens involved. Depending on the particular population of lymphocytes assembled, the disposal mechanism can be enhanced, suppressed or caused to change direction. The rules that govern the assembly of a particular immune organ are the focus of intense investigation. Cellular surface structures are involved, including histocompatibility antigens. So is the prior immune history of the host.*

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Based on a presentation at the Second UNC Symposium on Sarcoidosis, Asheville, North Carolina, October 7-9, 1983.

ed. In part this is accomplished locally by one of the populations of lymphocytes, the B cells, which bear on their surface membrane the particular immunoglobulin the B cell synthesizes. For some antigens, particularly carbohydrates (including lipopolysaccharides), specific B cells can be directly stimulated *in situ*. But the macrophage has a role in this processing as well. Not only can it digest and degrade the phagocytized X, but it can translate the disposal event into an information processing event. The macrophage, digesting this immune complex, becomes "activated." Some activated macrophages serve an accessory function in the stimulation of specific B cells to produce antibody. Some are particularly effective in stimulating T cells by means of secreting a lymphokine such as interleukin-1. There are many varieties of T cells. Some, when specifically stimulated, can help enhance the response of the B cell. Some can interact with X directly. (For example, there are some forms of T cells that are able to kill living cellular targets and even modify viral antigens.) And finally there are varieties of T cells that appear to have principally a modulating role in that they can turn off or turn down certain components of a specific immune response. All of this complexity is occurring *in situ*, in the extracellular space, in the presence of the noxious X.

Essentially an "immune organ" is established at the site of intrusion of the barrier defense mechanism. This immune organ is carefully modulated and designed to specifically dispose of the intruding foreign material. I call it an "organ" because it represents the careful orchestration of intercellular reactions among several components of the immune system including various types of lymphocytes and macrophages. They must all work together. Certain components probably fit together in order to function efficiently. Part of this efficient interaction is specific to the particular X but surface molecules other than antigen receptors interact in forming the immune organ. For example, these cells need to be matched as regards histocompatibility antigen to function efficiently. Of course that is not an issue in a given host (where all cells are matched) but it underlies the insights we are seeking when we attempt to discern an association between a particular histocompatibility antigen and a particular disease state. There are individual differences in surface glycoproteins on many cells including the cells that will form the immune organ. Since these surface molecules are involved in the fine structure of the immune organs, individual differences may lead to differences in the function that results from these cellular interactions.

All of this is health! What can go awry to cause sarcoidosis?

1. What would happen if X were indigestible, i.e. non-biodegradable! For some relatively inert materials such as a bentonite bead or a talc particle, the macrophage attempts or even accomplishes phagocytosis but digestion is impossible. What follows is the next clue to the sophistication of the macrophage as a pivotal cell in the formation of an immune organ. The presence of this non-degradable material in the phagolysosome causes the cell to recruit other macrophages presumably by producing chemotactic substances. There results, about this non-degradable particulate material, a rim of macrophage-like cells that we term a granuloma. For many such insults this response is not particularly aggressive and may well underlie the few granuloma that all of us have in our spleens and liver.

2. Sometimes the sequence just outlined is observed to be a bit more aggressive. For example if the bentonite bead is coated with antigen and allowed access to the pulmonary bed or liver of an animal that has previously been immunized with that antigen then a larger, more impressive, more cellular granuloma is seen to form.[1] Furthermore the cellular components are far more varied including cells that appear to be macrophages and others that clearly are in the lymphocyte line. Since the material is essentially nondisposable, there results a granuloma but again there need not be major destruction or even illness.

3. But there are circumstances where this scenario is not at all benign. Take the example of inhalation of silica particles that breach the barrier defenses of the alveoli. Silica particles are non-biodegradable and also toxic to cells. In the extracellular fluid they are protein-coated and phagocytized. Once inside the macrophage the protein coating is digested but the particle remains and literally destroys the macrophage from within.[2] A similar sequence of events occurs with crystals of monosodium urate. In both the silica story and the urate story granulomas form in the extracellular space. In the case of silica the granulomatous response is not well modulated and an interesting turn of events follows: namely, these damaged and dying macrophages put out factors that recruit additional macrophages as well as recruit fibroblasts and even stimulate them.[3, 4] A fibrosing granulomatous process occurs. The urate granuloma is equally impressive although the form of pathology is different. Here the macrophages produce communicating molecules that commandeer other cells in the ground substance. Interleukin-1 can stimulate catabolic processes by chondrocytes and in concert with osteoclast activating factor (OAF) can provoke an expanding lesion of bone and cartilage destruction we call a tophus.

4. The non-biodegradable substances capable of producing granulomatous inflammation are not that rare. Silica and urate are two examples. The microbial world is replete with such materials.[5] Notably, bacterial cell walls from particular species can provoke chronic granulomatous inflammation. Depending on the animal and the particular bacterium from which the wall was isolated as well as the form of the wall, one can use non-degradable bacterial cell wall peptidoglycan-polysaccharide fragments to provoke chronic granulation tissue in the heart, or skin, or liver, or even joints.[6]

5. Finally "non-biodegradability" may be more subtle than the physical construct postulated for the examples cited above. Berylliosis is an example of a systemic granulomatous disease with many features in common with sarcoidosis. Here the beryllium is thought to modify endogenous proteins throughout the body creating foci that appear to behave as if non-biodegradable particulate material was present.[7] Zirconium granulomata that plagued some individuals using zirconium-containing underarm deodorants was probably the result of a similar mechanism.[8] Although modification of endogenous proteins to create moieties that behave as if they are non-biodegradable is certainly possible, for me it is more appealing to think of sarcoidosis in the light of the previous examples.

Experimental immunology appears to be on the verge of answering the critical questions related to the pathogenesis of sarcoidosis. We need to determine what "non-biodegradable" material is in the center of all these granulomas. Perhaps more importantly, we need to understand how granulomas are modulated (in the sense of the schema in figure 1). The "activated macrophages" that comprise the sarcoid granuloma wherever they are found seem to be displaying an array of functions beyond just attempting to dispose of the putative non-degradable material. They are recruiting and stimulating fibroblasts; witness the pulmonary and myocardial fibrosis. In bone they are activating osteoclasts to produce the characteristic lytic lesions. They produce a family of molecules called Interleukin-1 which not only activates T cells but functions as the long sought "leukocyte pyrogen."[9] They develop the potential to participate in vitamin D metabolism; this function may explain the hypercalcemia of sarcoidosis and the observation that hypercalcemia can persist in an anephric sarcoid patient.[10] Activated macrophages synthesize and boldly secrete an abundance of enzymes and other proteins[11] such as complement components, proteases, lysozyme, and angiotensin converting enzyme.[12] The sarcoid granuloma is indeed an immune endocrine organ, an integrated heterogeneous grouping of cells producing a myriad of factors that influence each other's function and that of cells residing near and far. If we understood these endocrine processes, we might be able to teach the host to be less aggressive in the granulomatous response; clearly normal tissue is paying the price we call sarcoidosis.

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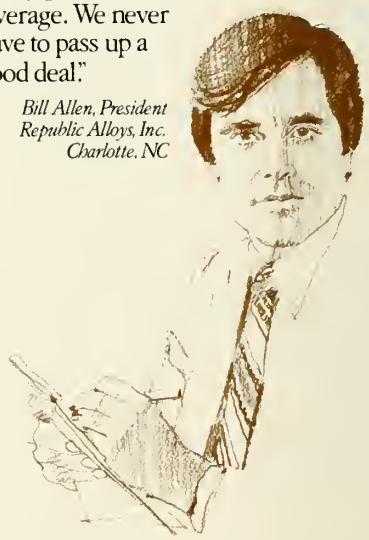
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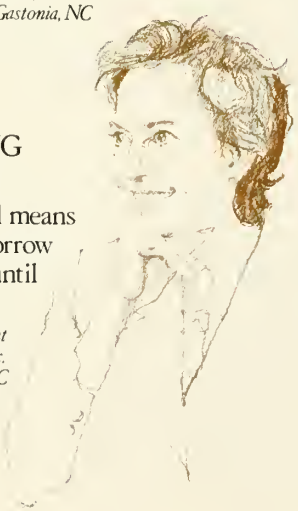
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Things I Know and Things I Don't Know: How to Develop a Better Opinion

David L. Simel, M.D.

WHEN I ask for help from a colleague, sometimes I want facts and sometimes I want opinions. However, I always want my consultant's opinions to have roots in facts. Since opinions are only educated guesses I am more inclined to believe one truth than many half-truths.

A consulting internist's opinion was that my patient with unilateral leg swelling, pain, tenderness, and a Homan's sign had thrombophlebitis. I concurred and was pleased we agreed since his opinion was based on more experience than mine; experience should make us wiser. We learned a truth when the radiologist discovered occlusive iliac vein disease by venography. My guess that thrombophlebitis existed was only based on my youthful experience, not facts. A factual opinion would have required knowing the correlation between symptoms, signs, and disease, not from the untested experience of wiser physicians, but from the published facts of controlled clinical trials. When I force myself to learn facts I can develop better opinions, ask better questions, and learn more from my own anecdotes. If I do not learn to separate truths from half-truths I deceive myself by thinking I know what I really do not.

I was recently asked whether or not to give a young lady streptokinase for deep venous thrombosis. My opinion was yes, but I could not support it with facts. She did quite well receiving fibrinolytic therapy; perhaps she and I were lucky. I subsequently read the literature which compares streptokinase to heparin. Eight weeks later (acquiring facts to develop opinions cannot always be done quickly) I learned what is known about venous thrombi and the clinical use of streptokinase. More important, I know what I do not know and I can ask intelligent questions to those who say they do.

I reviewed about three-dozen clinical studies (no case reports) that used fibrinolytic therapy for deep venous thrombosis. Using a method taught by others I critically appraised each article for certain criteria (table 1).[1] I looked for studies that had specific inclusion and exclusion criteria reflecting what I see in my patient population. The diagnosis had to be confirmed by venogram so that the therapeutic benefit could be attributed to treatment of definite disease. Since I wanted a comparison between two therapeutic modalities, I expected 1) the patients to be successfully randomized to heparin or streptokinase, 2) the treatment method specified in enough detail that I could reproduce it in my own patients, and 3) blinded treatment administration and outcome assessment so that I knew the results were not biased. The follow-up period had to be long enough to be clinically meaningful. I committed my appraisals to paper so that my thoughts would be retrievable. Very few studies came close to meeting my requirements for a good clinical investigation; but there was always something useful in the act of reading poorly designed trials: I learned to recognize truths and half-truths. I was able to accept and modify recent recommendations for the use of thrombolytic therapy. (See tables 2, 3.)

Table 1
Criteria for Critical Appraisals

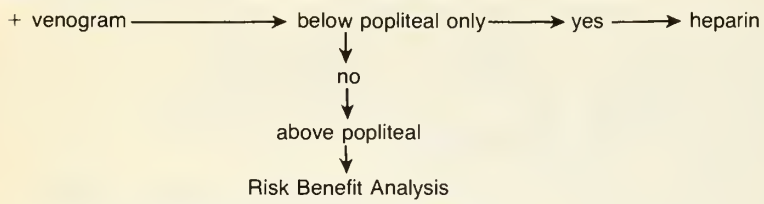
1. Patient selection criteria
2. Diagnostic criteria
3. Prognostic stratification
4. Therapeutic maneuver
5. Blind treatment administration
6. Verification of potential therapeutic benefit by plasma assays
7. Patient allocation method
8. Outcome criteria
9. Blinded outcome assessment
10. Appropriate follow-up period
11. Statistical method

The two studies that came closest to passing my critical appraisal found that streptokinase yielded a clinically normal leg in about three-fourths of patients versus heparin which gave a normal result in only one-third (see table 4). The venographic findings were normal in forty-four percent of patients who received streptokinase, but no patients treated with heparin regained normal venous anatomy. Though another forty-four percent of streptokinase patients had major post-thrombotic venogram changes, none had serious clinical findings. Twelve percent of patients treated with streptokinase had only slight post-thrombotic changes. Two-thirds of the heparin-treated patients had major post-thrombotic venogram changes and one-third had slight changes. Other studies that came close to passing critical appraisal yielded comparable results.[5, 6]

I developed some opinions: 1) that streptokinase is more likely to give the results I would like for my own legs, but 2) that there must be other determinants in the development of the clinical post-thrombotic state besides complete thrombolysis since some patients with no signs or symptoms will have an abnormal venogram years later. I think that there is a greater tendency to serious hemorrhage from fibrinolytic therapy (perhaps 10-15% for streptokinase versus 5% for heparin) but I do not know that since there is an appreciable

From the Department of Medicine, Duke University Medical Center, Durham 27710.

Table 2
Guidelines for Lytic Therapy



Absolute Contraindication	*Relative*	*Intangibles*
Active bleeding	Pregnancy	Post-thrombotic sequelae
Recent (within 2 months)	Menses	Prior deep venous thrombosis
Cerebrovascular accident	Recent (less than 10 days)	Age
intracranial process	Surgery	Co-morbid illness (e.g., decreased life
	Post-partum	expectancy)
	Organ Biopsy	Symptoms greater than 7 days
	Puncture noncompressible vessels	
	Peptic ulcer disease or history of gastrointestinal hemorrhage	
	Course of streptokinase in past year	
	Recent trauma	
	Blood pressure greater than 200 mm Hg systolic or 110 mm Hg diastolic	
	Recent trauma or cardiopulmonary resuscitation	
	Hemostatic defects (including liver or renal disease)	
	High likelihood of left heart thrombus	
	Endocarditis	

From Sharma GVRK, Cella G, Parisi AF, Sasahara AA: Thrombolytic therapy. NEJM 1982;306:1268-1276.

range of complications reported in these three dozen differently designed and controlled studies. Streptokinase therapy is about five times as expensive as heparin, but the cost of fibrinolytic therapy is certainly not prohibitive.

A patient with recurrent deep venous thrombosis poses therapeutic dilemmas. If the patient had previously been treated with heparin rather than streptokinase, the leg would probably have had an abnormal venographic appearance if studied prior to the recurrent clot (see table 4). A patient with deep venous thrombosis who already had post-thrombotic sequelae would most likely not receive much benefit from fibrinolytic therapy and I would prescribe anticoagulation. What if the patient with recurrent deep venous thrombosis, whose initial event was treated with heparin, was fortunate enough to be among the one-third of such patients returning to clinical normality (see table 4)? Whatever it was that made such a patient have normal legs despite abnormal anatomy, I would want the legs to be like they were before the recurrent thrombus: fibrinolytic ther-

Table 3
Guidelines for Lytic Therapy

If risk-benefit analysis is acceptable for treatment:

1. Stop heparin if patient already on it
2. Pre-lytic labs: TCT, aPTT, PT, Hct, platelet count. (If patient has been on heparin; fibrinogen, FDP).
3. During Treatment:
   Blood work during treatment with 22 or 23 g needle
   Bed rest
   Pressure dressings
4. Vital signs every four hours
5. Hydrocortisone 100 mg IV before treatment, then po q 12-24 hrs. SK 250,000 μ bolus/30 minutes then 100,000 μ/hr × 72 hrs
6. 3-4 hours after bolus check TCT or aPTT
7. If no change, re-bolus with 250,000 μ and continue the infusion. Recheck TCT or aPTT. If still no response, use urokinase or heparin.
8. Stop treatment at 72 hrs, wait 3-4 hrs and recheck TCT or aPTT. When aPTT 2x control, begin heparin without loading dose.

Abbreviations: SK — Streptokinase, BP — blood pressure, TCT — thrombin clot time, aPTT — activated partial thromboplastin time, PT — prothrombin time, Hct — hematocrit, FDP — fibrin degradation products.

From Sharma GVRK, Cella G, Parisi AF, Sasahara AA: Thrombolytic therapy. NEJM 1982;306:1268-1276.

Table 4
Treatment Outcome

	Treatment (Percent) Streptokinase	Heparin
Venogram		
Normal	44%	0%
Slight post-thrombotic changes	12%	33%
Major post-thrombotic changes	44%	67%
Clinical Exam		
Normal	76.5%	33.3%
Moderate Signs edema, varicosities, or pigmentation	23.5%	50%
Serious Signs (leg ulcer)	0%	16.7%

From Arnesen H, Hoiseth A, Ly B: Streptokinase or heparin in the treatment of deep vein thrombosis. Acta Med Scand 1982;211:65-68.

apy is much more likely to restore the pre-existent anatomy than heparin.

I do not believe we are administering fibrinolytic therapy the safest way possible and hope that we will find a way to administer it with fewer complications. An innovative treatment protocol combining intermittent streptokinase with plasminogen suggests that there are better regimens.[7] If we can maintain the therapeutic efficacy of fibrinolytic agents, keep the cost from appreciably rising, and lower the complication rate even further, choosing between streptokinase and heparin will become easy since fibrinolysis will almost always be preferred.

Though I was specifically interested in developing better opinions about the clinical comparison between streptokinase and heparin, simple osmosis expanded my data bank. I learned about plasminogen and the fibrinolytic system, noninvasive assessment of venous function, hemostatic tests, and the cost of the severe post-thrombotic syndrome. I understand that it must be difficult to formulate a well-designed study, but my opinions will be better now that I am able to recognize what is truth and what is a half-truth.

I hope my consultants do not become frustrated if I ask for the facts supporting their opinions. My own consulting opinions given to my colleagues can now have an appropriate amount of authority since I will be more aware of what I know and what I don't know. Factual opinions do not have their roots in just clinical experience, but are based on critical appraisals and analytic thought. The next patient receiving streptokinase from me will be under the care of a much smarter physician than that lucky young lady.

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References:

1. Stone PH, Turi ZG, Muller JE. Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104 672-681, September 1982.
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BRIEF SUMMARY
PROCARDIA® (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents. (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients; transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

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3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

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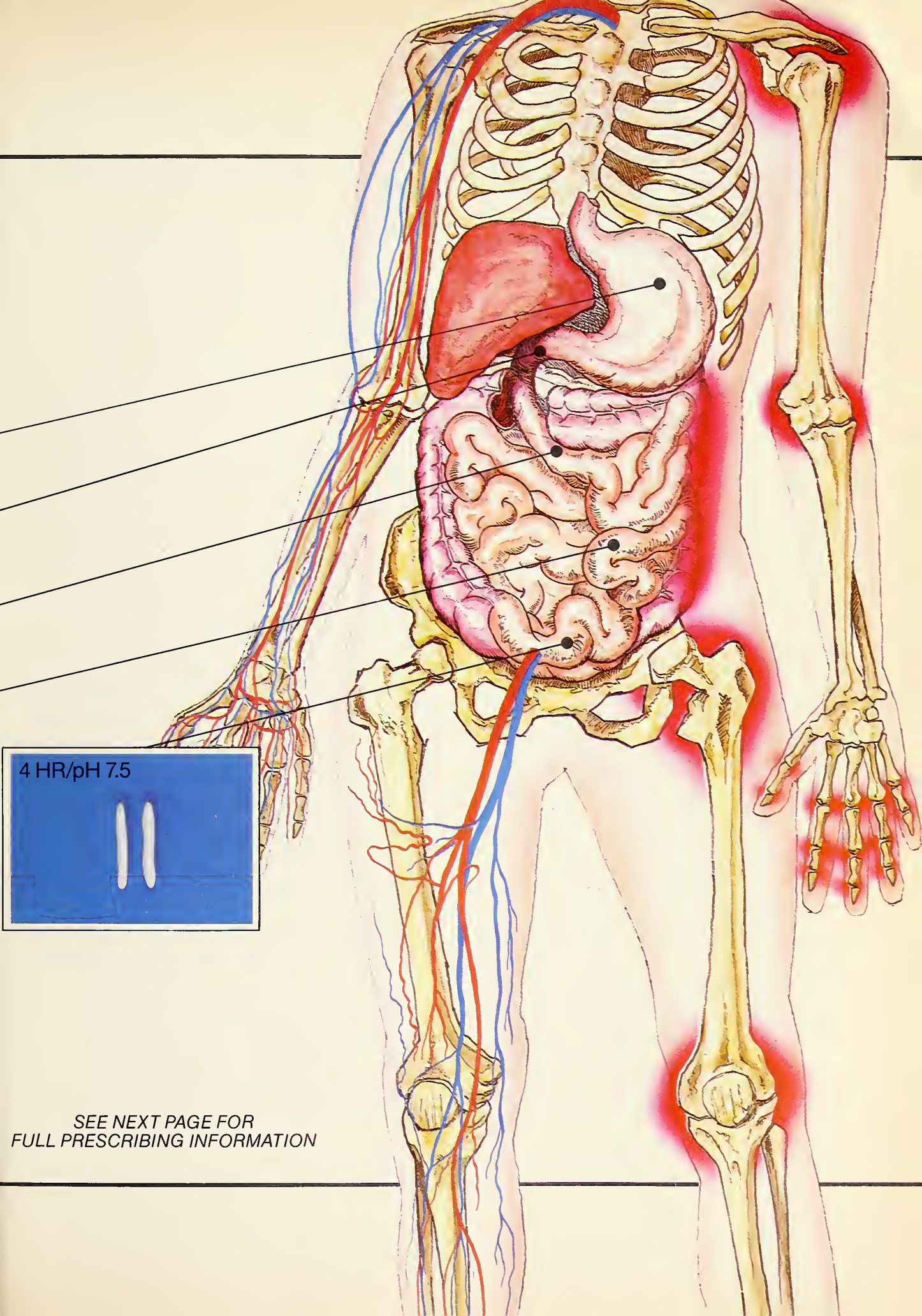


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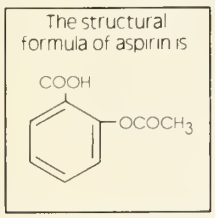
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FULL PRESCRIBING INFORMATION

ZORprin (ASPIRIN) Zero-Order Release

DESCRIPTION: Each capsule-shaped tablet of Zorprin contains 800 mg of aspirin, formulated in a special matrix to control the release of aspirin after ingestion. The controlled availability of aspirin provided by Zorprin approximates zero-order release, the *in vitro* release of aspirin from the tablet matrix is linear and independent of the concentration of the drug. □ **CLINICAL PHARMACOLOGY:** Aspirin, as contained in Zorprin, is a salicylate that has demonstrated anti-inflammatory and analgesic activity. Its mode of action as an anti-inflammatory and analgesic agent may be due to the inhibition of synthesis of prostaglandins, although its exact mode of action is not known. □ Zorprin dissolution is pH-dependent. *In vitro* studies have shown very little aspirin to be released in acidic solutions, whereas, Zorprin releases the majority of its aspirin (90%) in a zero-order mode at a neutral to alkaline pH. It is this pH dependence of Zorprin that reduces direct contact between aspirin and the gastric mucosa, resulting in a reduction of its gastrointestinal side-effect potential. □ Bioavailability data for Zorprin have confirmed that plasma levels of salicylic acid and acetylsalicylic acid can be measured 24 hours after a single oral dose. This substantiates a twice daily dose regimen. Multiple dose bioavailability studies showed similar steady-state salicylate levels for Zorprin as for conventional release aspirin using the same total daily dose. Long-term monitoring of salicylate levels showed no signs of accumulation once steady-state levels were reached (4-6 days). □ Studies of *in vivo* prostaglandin levels (PGE2) have shown Zorprin plasma levels of salicylic acid and acetylsalicylic acid to reduce PGE2 levels 14 hours after a single oral 800 mg dose while an equivalent dose of aspirin produced a reduction of PGE2 levels only through six hours. Zorprin's effect on prostaglandins other than PGE2 has not been determined. □ Salicylates are excreted mainly by the kidney, and from studies in humans it appears that salicylate is excreted in the urine as free salicylic acid (10%), salicyluric acid (75%) salicylic phenolic (10%), acyl glucuronides (5%) and gentisic acid (<1%). □ **INDICATIONS & USAGE:** Zorprin is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of Zorprin have not been established in those rheumatoid arthritic patients who are designated by the American Rheumatism Association as Functional Class IV (incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care). □ In patients treated with Zorprin for rheumatoid arthritis and osteoarthritis, the anti-inflammatory action of Zorprin has been shown by reduction in pain, morning stiffness and disease activity as assessed by both the investigators and patients. □ In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Zorprin has been shown to be comparable to conventional release aspirin in controlling the aforementioned signs and symptoms of disease activity and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS). Zorprin may be well tolerated in some patients who have had gastrointestinal side effects with conventional release aspirin, but these patients when treated with Zorprin should be carefully followed for signs and symptoms of gastrointestinal bleeding and ulceration. □ Since there have been no controlled trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of Zorprin in conjunction with other nonsteroidal anti-inflammatory agents (NSAI), the combination cannot be recommended (see **Drug Interactions**). □ **Because of its relatively long onset of action, Zorprin is not recommended for antipyresis or for short-term analgesia.** □ **CONTRAINDICATIONS:** Zorprin should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema, bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. Zorprin is not recommended for children under 12 years of age, it is contraindicated in all children with fever accompanied by dehydration. □ **WARNINGS:** Zorprin should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress platelet aggregation and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics, concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. □ While salicylates in large doses have a uricosuric effect, smaller amounts may reduce water excretion and increase serum uric acid. □ USE IN PREGNANCY. Aspirin can harm the fetus when administered to pregnant women. Aspirin interferes with maternal and infant hemostasis and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. □ If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. □ Aspirin should not be taken during the last 3 months of pregnancy. □ **PRECAUTIONS:** Appropriate precautions should be taken in prescribing Zorprin for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing Zorprin for those patients with bleeding tendencies or those on anticoagulants. □ In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when Zorprin is made a part of the treatment program. □ Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by dosage reduction. □ Salicylates can produce changes in thyroid function tests. □ Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery. □ Since aspirin release from Zorprin is pH dependent, it may change in those conditions where the gastric pH has been increased as a result of antacids, gastric secretion inhibitors or surgical procedures. □ **Drug Interactions:** (See **WARNINGS**) Aspirin may interfere with some anticoagulant and antidiabetic drugs. Drugs which lower serum uric acid by increasing uric acid excretion (uricosurics) may be antagonized by the concomitant use of aspirin, particularly in doses less than 2.0 grams/day. Nonsteroidal anti-inflammatory drugs may be competitively displaced from their albumin binding sites by aspirin. This effect may negate the clinical efficacy of both drugs. Also, the gastrointestinal inflammatory potential of nonsteroidal anti-inflammatory drugs may be potentiated by aspirin. The combination of alcohol and aspirin may increase the risk of gastrointestinal bleeding. □ Aspirin may enhance the activity of methotrexate and increase its toxicity. □ Sodium excretion produced by spironolactone may be decreased in the presence of salicylates. Concomitant administration of other anti-inflammatory drugs may increase the risk of gastrointestinal ulceration. Urinary alkalinizers decrease aspirin's effectiveness by increasing the rate of salicylate renal excretion. Phenobarbital decreases aspirin's effectiveness by enzyme induction. □ **Pregnancy Category D.** See **WARNINGS** Section. □ **Nursing Mothers:** Salicylates have been detected in the breast milk of nursing mothers. Because of the potential for serious adverse reactions from aspirin in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the benefit of the drug to the mother. □ **ADVERSE REACTIONS: Hematologic:** Aspirin interferes with hemostasis. Patients with a history of blood coagulation defects or receiving anti-coagulant drugs or with severe anemia should avoid Zorprin. Aspirin used chronically may cause a persistent iron deficiency anemia. □ **Gastrointestial:** Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from Zorprin is designed to occur in the small intestine over a period of time. This has resulted in fewer symptomatic gastrointestinal side effects. □ **Allergic:** Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. Fatal anaphylactic shock, while not common, has been reported. □ **Respiratory:** Aspirin intolerance, manifested by exacerbations of bronchospasm and rhinitis, may occur in patients with a history of nasal polyps, asthma, or rhinitis. The mechanism of this intolerance is unknown but may be the result of aspirin-induced shunting of prostaglandin synthesis to the lipoxygenase pathway and the liberation of leukotrienes, e.g. slow-reacting substance of anaphylaxis. □ **Dermatologic:** Hives, rashes, and angioedema may occur, especially in patients suffering from chronic urticaria. □ **Central Nervous System:** Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. □ **Renal:** Aspirin rarely may aggravate chronic kidney disease. □ **Hepatic:** High doses of aspirin have been reported to produce reversible hepatic dysfunction. □ **OVERDOSAGE:** Overdosage, if it occurs, would produce the usual symptoms of salicylism: tinnitus, vertigo, headache, confusion, drowsines, sweating, hyperventilation, vomiting or diarrhea. Plasma salicylate levels in adults may range from 50 to 80 mg/dl in the mildly intoxicated patient to 110 to 160* mg/dl in the severely intoxicated patient. An arterial blood pH of 7.1 may indicate serious poisoning. The clearance of salicylates in children is much slower than adults and should receive due consideration when aspirin overdosages occur in infants, salicylate half-lives of 30 hours have been reported in infants 4-8 months old. Treatment for mild intoxication should include emptying the stomach with an emitic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of sodium bicarbonate and dextrose or sodium lactate. In extreme cases, hemodialysis or peritoneal dialysis may be required. □ (*A plasma salicylate level of 160 mg/dl in an adult is usually considered lethal.) □ **DOSAGE & ADMINISTRATION:** *In order to achieve a zero-order release, the tablets of Zorprin should be swallowed intact.* □ *Breaking the tablets or disrupting the structure will alter the release profile of the drug.* □ *It is recommended that Zorprin be taken with sufficient quantities of fluids (8 oz. or more).* □ **Adult Dosage:** For mild to moderate pain associated with rheumatoid arthritis and osteoarthritis, the recommended initial dose of Zorprin is 1600 mg (2-800 mg tablets) twice a day. Because of Zorprin's prolonged release of aspirin into the bloodstream, Zorprin tablets may be taken as a b.i.d. dose. Further adjustment of the dosage should be determined by the physician, based upon the patient's response and needs. Since it will take 4-6 days to reach steady-state levels of salicylic acid with Zorprin, it is recommended dosages be given for at least one week before further adjustment. In general, patients with rheumatoid arthritis seem to require higher doses of Zorprin than do patients with osteoarthritis. □ **Zorprin is not recommended for children below the age of 12.** □ **HOW SUPPLIED: Zorprin Tablets 800 mg;** plain, white capsule-shaped tablets. □ Bottles of 100 Tablets —NDC 0524-0057-01 □ **Caution:** Federal law prohibits dispensing without prescription. □ U.S. Patent No. 4,308,251. □ **Manufactured and Distributed by: BOOTS PHARMACEUTICALS, INC., Shreveport, Louisiana 71106 U.S.A.**



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Atrial Fibrillation With Long Survival

William Harding Kneedler, M.D. and John J. Guyer, M.D.

A TRIAL fibrillation is common in hearts with a variety of identifiable disease states. At times the presence of atrial fibrillation is the only abnormality indicating that a particular heart is different from what we call a normal heart. While we do not know the reason for the difference, the absence of sinus rhythm informs us that a difference is present. Observation teaches us that in certain instances the structural change accounting for fibrillation is non-progressive and that the prognosis of the patients with this undetectable structural change is different from that present in hearts damaged by known disease processes. Friedberg[1] reported that 5 to 6% of atrial fibrillation occurs in hearts with no other findings. White[2] said, "Sometimes violent exertion and excitement are responsible for the onset of paroxysmal or permanent atrial fibrillation with little or no heart disease." In some instances, intermittent atrial fibrillation may become permanent.

In some family groups there is a familial tendency. White[3] said, "Several members of a family may be affected, even in youth, without serious heart disease, and in fact in some cases without any disease at all." Friedberg[1] reported two brothers and the 28-year-old son of one of them as having recurrent atrial fibrillation with no other evidence of cardiac abnormality.

Atrial fibrillation in the presence of valvular and myocardial diseases lowers the efficiency of the heart as a pump. In their absence, patients with atrial fibrillation may live many years. No studies have been done in this group to measure the efficiency of the fibrillating heart. When the senior author was an intern at the Pennsylvania Hospital, the hospital barber told him that he had had atrial fibrillation continuously for 40 years. He examined him and found the heart totally irregular. This man died in congestive heart failure about a year later. White reported a case of atrial fibrillation of over 30 years' duration, and one of flutter of over 40 years' duration whom he had followed for 32 years and who had enjoyed constant good health. This woman was 77 and still in good health when he made his report.

The person whose story we wish to report here had atrial fibrillation for more than 60 years during which time he enjoyed good health and never showed any sign or symptoms of heart disease.

Muang Chai Chainilpant of Chiang Mai, Thailand, a medical practitioner, developed total cardiac irregularity while playing badminton in 1905 or 1906 at the age of 20. His heart remained totally irregular thereafter until he died very early in 1968 at the age of 82. Dr. E. C. Cort followed him for many years, considering the condition to be atrial fibrillation. The senior author first checked him in 1931 and followed him through 1941, seeing him again in 1949-51 and during 1967. His heart was always totally irregular. The junior author first saw him in 1957 for irregular heart and hypertension and followed him until his death from a CVA in 1968. No electrocardiograph was available until 1958, at which time ECG showed the typical findings of atrial fibrillation and continued to do so thereafter.

At least three other members of this man's family also have had atrial fibrillation, including a son, a nephew and a niece. The niece, now 53, had intermittent atrial fibrillation for five years followed by permanent atrial fibrillation for the past 15 years.

We believe that this case of atrial fibrillation, with survival for more than 60 years, represents the longest survival with this condition continuously on record.

From 234 Scenic Drive NE, Concord 28025 (Dr. Kneedler) and Chiang Mai, Thailand (Dr. Guyer).

References

1. Friedberg C: Disease of the Heart, 3rd ed., 1966, p. 538.
2. White P: Heart Disease, MacMillan, 1951, p. 900.
3. White P: Hearts, Their Long Followup, Saunders, 1967.

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The State of Medicine in 1912*

J. C. Walton, M.D.

IN the springtime of 1879 two verdant young country medicos might have been seen wending their sad journey to Greensboro to undergo that terrible ordeal, an examination before the State Board of Medical Examiners. The writer will never forget what fear and trembling possessed his soul when first confronting that august body and his unbounded joy and enthusiasm when told that he had passed.

My friend in misery was Dr. Charles E. Bradsher of Person County, North Carolina who later became the leading physician in that section of this State and but for an early death from the great white plague might easily have adorned and graced any position in this honorable body.

Dr. Bradsher was a born physician and the most resourceful one that I have ever known. I recall on one occasion when called to relieve a small boy suffering from retention, the doctor not having a catheter and the case being very urgent, he improvised an instrument from a feather and saved the day. On another occasion when called to see a man who was seriously hurt in a drunken brawl he found a fractured skull and a bad fracture and dislocation of one of the extremities; after raising the depressed bone the patient became conscious and then attempting to relieve the limb the man became so unmanageable that the good doctor depressed the bone on his skull and he became quiet and unconscious, and after dressing the limb the doctor again lifted the fragment off the skull, the man became conscious and made an uneventful recovery. You can readily perceive that no anaesthetic was available and the doctor's ingenuity had to meet the issue. In other words, the man and the occasion met.

From the above you will readily see that the life of the country doctor tends to develop the qualities of resourcefulness and of self-reliance. I know of no better training school for the recent graduate in medicine than five or ten years of country work. It will make a good physician of him, if anything will.

After securing our licenses we were so elated that my friend Bradsher thought that the next thing in order was to have some visiting cards struck off with the honorable distinction thereon: "Member of the State Medical Society," as we were the pioneer Board Tacklers from the respective counties of Person and Caswell, we did not like to hide our light under a bushel, but after a little reflection and time to allow our enthusiasm to cool we reluctantly decided to forgo this honor, lest it might be thought by our friends to savor of charlatanism.

In the olden days the medicos were not afflicted with the surgery craze but they were taught the most important and useful branches. The ones they would need most in their daily work, viz.: practice of medicine, obstetrics, materia medica, therapeutics, and physical diagnosis as in those days the doctor was required to diagnose and to treat his own patients secundem artem, otherwise he would soon find himself in the position of a doctor without a patient.

Per contra — in these modern, up-to-date times every medico is a born surgeon. The good old branches are obsolete and the old family doctor has become a tradition in this age of specialism and agnosticism.

It is considered by many to be an indication of culture to be an unbeliever, a scoffer and a doubter — even the good old family Bible is losing caste and is being relegated from its seat of honor on the center table in our parlors — to the garret.

Should God's last and best gift to man become ill, she visits a specialist, an internal medicine man, who probably has had good laboratory facilities, but lacks clinical experience and the saving grace of common sense. This gentleman in order to sufficiently impress her of his great and transcendental importance takes down a long clinical history and she gets a gastric, urinary, fecal and blood ex. et al., etc.

For her headaches she is referred to an ophthalmologist, gets a mydriatic and is told to use glasses. For the pain in her abdomen she is sent to the omniscient and omnipotent surgeon who finds that she has appendicitis and that her gallbladder needs draining. Possibly her uterus is slightly displaced, for which she needs a ventral fixation, curettage, etc. After emerging from all this, a shadow in body and mind, the neurologist gets her and she continues the downward route and like the woman mentioned in the Scriptures, suffered much at the hands of many physicians.

Her resources being about exhausted, and likewise having exhausted scientific medicine, like a drowning person she catches at a straw and seeks solace in Christian Science when she is comforted with the good news that there is no such thing as sickness, disease or death.

Gentlemen, are we wholly to blame for this unfortunate state of affairs? If we would cling closely to the ideals of the fathers and always consider the interest of the patient paramount, there undoubtedly would be less of quackery and charlatanism.

We all realize that medical overloading is bad and the more doctors who are called in to see a case the less is the individual interest and responsibility felt by each one of them.

Erichsen taught that a man should be in general practice twenty years before adopting a specialty and in my student days, ten years' general work was considered necessary

* Excerpted from a paper published in the June 19, 1912 *Transactions of the North Carolina Medical Society*.

fore specializing. I believe that after graduating, one or two years as an intern in a general hospital followed by two or three years of country work would sufficiently broaden one's perspective to make him eligible for special work.

THE MORE THINGS CHANGE, THE MORE THEY STAY THE SAME

The State of Medicine in 1983
The Extinction of the Physician

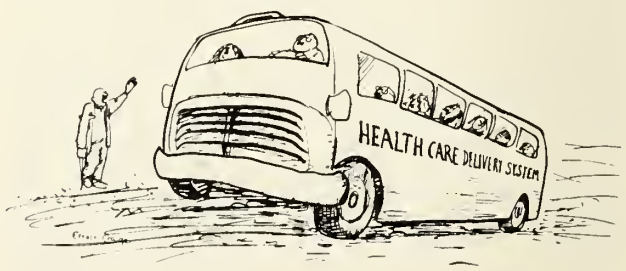
Nortin M. Hadler, M.D.

FOR all of us who practice medicine by choice and to the best of our ability, this is a perplexing time, a time of paradox. We have more to offer our individual patients than at any time in the history of medicine, yet society does not seem to champion our role. As I continue to ponder this paradox, I'd like to share some of my perceptions in the hope they are insights.

After World War II, science was ripe for application to medicine and society was ready. Commencing with the Truman administration, federal monies began to flow into the medical schools for the training and sustenance of clinical investigators. For the first time, young doctors with skill, interest, talent, and commitment saw no financial barriers to pursuing a career in investigative medicine. The result was the golden age of clinical investigation which thrived with little distortion into the early 1970s. As a result, we possess a pharmacopoeia brimming with agents that are effective if used appropriately, a technological armamentarium for diagnosis and life support that boggles the mind, and a surgical craft approaching the limits of macroscopic manipulation. The fate of academic departments dedicated to clinical investigation is a tragic spectre upon which I have expounded elsewhere (De Morte Medicinae, *Clinical Research,* February, 1984). More germane to this discussion is the fashion in which they functioned in their heyday.

In these departments and in the medical schools they came to dominate, the clinical investigator assumed preeminence. To test one's inferences relative to the pathophysiology of disease or, secondarily, to its treatment, was clearly the highest calling to which a physician could aspire. Throughout the fabric of Western medicine, there is no argument against this tenet. Such a role, however, was not only the most laudable pursuit; it was the only pursuit worthy of high praise. The acclaim garnered by previous generations of physicians for their astuteness at the bedside, for their reasoning on behalf of the patient seen one at a time, for their clinical categorizations, and for their compassion and stature was silenced. The physician was now called a "clinician" to distinguish him from the investigator, was downgraded to second-class citizen in the academy and often vanquished. There was no protest; the accomplishments of the investigative establishment were brilliant, overpowering, and ethical. The clinician had to applaud. He also had to await and exploit every advance that was forthcoming.

These events, largely laudable, carried with them a second agenda. The precedent for expending large sums of federal money on medical education and clinical investigation was set. Simultaneously, the academic establishment let it be known that investigation was their calling, their dream come true. All else in their traditional purview was secondary. The stage was set for the development of an efficient, global, egalitarian means of making the dramatic advances of investigative medicine available and for accomplishing the aspects of patient care considered more mundane. And the stage was set by individuals whose backgrounds and proclivities gravitated toward administration and policy formulation. The "health care delivery system" was born. The size and scope of the "system" is far beyond the richest imagination in 1950. Of course, it infected and converted the medical schools. Our leading institutions prefer to be called "academic health (or medical) centers," conglomerates of many schools, disciplines, hospitals and missions (Lewis IJ, Sheps CG: *The Sick Citadel,* Oelgeschlager, Gunn & Hain, Cambridge, Mass., 1983).



An ill individual may still turn to and value his physician. But in the minds of health care planners, the physician is weighted as simply one resource, option or component. Even the academic medical center doesn't strive to nurture such an individual. Instead, patients are treated to and by a

From the Departments of Medicine and Microbiology, University of North Carolina School of Medicine, Chapel Hill 27514.

Illustrations by Ernest Craige, M.D.

health care delivery system. Doctors themselves are too skilled, too highly trained, and too scientific to be expected to help patients cope with the impact of their disease on their life, with their illness. Doctors are to wield science and technology to treat and occasionally cure diseases, blind in their faith that such an effort will solve their patient's predicament. The system has cultivated minions to supplement the exalted and supposedly time-consuming efforts of the doctor: family nurse practitioners, physician assistants, social workers, a polymorphism of counselors and therapists (occupational, rehabilitation, physical, vocational, recreational, dietary to mention a few) and a burgeoning administrative structure with a life of its own. Perhaps the ultimate in this evolution is the production of less scientifically focused doctors who, admittedly and intentionally, pull back from the cutting edge of scientific medicine. "You can't learn it all, why try?" seems to be their banner. Their selling point, at best, is that they attempt to substitute skill and training in manipulating the impact of the disease on the patient's life; at worst, they offer only facility in manipulating the health care delivery system.

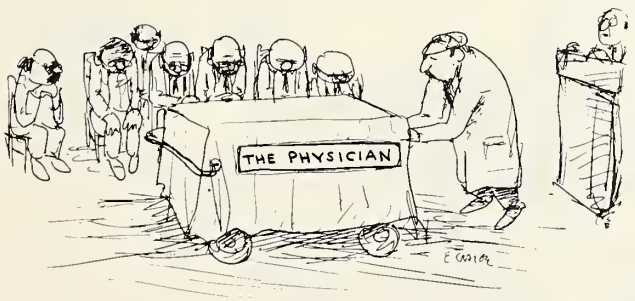
The current establishment speaks with one of two voices:

1. We are living in the golden age of applied science. The horizons are limitless. Scientific medicine will provide answers that will allow most of us to live out our full life expectancy free of morbidity.

2. Taking advantage of the past and future advances of medicine and its allied sciences requires yet a more efficient, more sophisticated and better designed health care delivery system that matches the possible with the feasible.

Of course, there is always a role for doctors; they are necessary to apply the most scientific and technological advances. They are as integral to the system as the medical school is to the academic health center. No one seems to have identified a niche, need or role for a personal physician any more. The system has become the substitute for the individual who is a student of the human predicament bringing to the bedside compassion, perspective, and science as a practitioner of the philosophy that was medicine.

The social realities are such that the process that will lead to the extinction of the physician appears inexorable. To reverse it, or even slow it down, requires cogent rebuttal of the two establishment arguments listed above:



1. Your hope is delusional. There is no technological solution to the human predicament. You may cure a disease or two but in the experience of illness disease is only one operating variable. The cure of an acute infection, the setting of a fracture, and the suturing of a wound are not particularly demanding undertakings. Consider the judgment necessary to administer a marginal therapy; consider the quandary of a patient with chronic inflammatory disease; consider the impact of the personal experience of any illness on family or in the workplace. Then tell me you see a solution on the horizon of molecular biology.

2. All systems have one serious flaw: they develop their own constituency. There will always be people who commit to the system rather than its output or mission. Making sure that a "health care delivery system" remains an infrastructure is an exercise that has seldom succeeded. Clearly the American system of today appears responsive to the interests and often greed of almost all groups involved. Only the individual patient, the solitary human being who is afraid, anxious, with functional incapacity or even in pain, has no defined advocate. He has no physician.

If American society desires to maintain a cadre of physicians, then there is an immediate need to re-examine the fashion in which we educate the next generation of physicians. The medical schools must be cleaved from the academic health centers and held accountable for the education of physicians and for maintaining the ethical fabric of medicine by example. Clinical departments belong in a medical school and must be excellent. The "basic sciences" are appropriately in the faculty of Arts and Sciences. All Arts and Sciences faculties are relevant to medical education; the universities must become aware of this and faculties learn to share and communicate. Medical students should enter with strong undergraduate grounding in the liberal arts as well as the sciences. Medical school should be a structured 7-year graduate curriculum (almost everyone spends at least 7 years in training anyway, 4 in medical school and 3 postdoctoral years). Exposure to natural and social sciences should be integrated with training in clinical application throughout the 7 years. The faculty should be laced with exemplary physicians teaching and taking many of these courses throughout their careers. The ethic they live is patent: "You can't learn it all, but you never cease trying." After 4 years students can opt for a career in bench science having enjoyed intensive exposure to human biology. After 7 years we will graduate a cohort of physicians all sharing the skills that we'd like to ascribe today to the primary care internist-pediatrician. Individuals who want to master and practice a technology as well (pathology, surgery, invasive procedures, etc.) will require further training. The period required, however, is limited since their education will already have been substantial and the need for perspective well ingrained.

There are many obvious stumbling blocks to such a radical change in medical education, from licensure issues to faculty remuneration. There are even more issues that are imponderable. But if we believe in the goal, all are surmountable. Doctors must be held accountable for their wisdom as physicians. Perhaps if we produce these neighborhood Maimonides, the absurdities of the health care delivery system and industry will become apparent to all and finally remedied. But for now, my elegy is appropriate.

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THE 18-HOUR-A-DAY DOCTOR

Dr. Gaine Cannon

A modern-day version of the country doctor on horseback, Dr. Gaine Cannon covered his scattered practice around the Blue Ridge Mountain country near Balsam Grove, North Carolina, in a four-wheel-drive Jeep wagon.[1]

On an average working day, Dr. Cannon rose at sunup to see patients at his converted-farmhouse clinic before setting out to make his usual 15 to 20 house calls around the countryside. Generally, after treating his primary patient, he saw each member of the family, as well—his personal effort at preventive medicine.

Multiple services

With the nearest hospital some 60 miles away and no pharmacy closer than an hour-and-a-half drive, Dr. Cannon filled his own prescriptions, delivered babies and treated many patients at a centrally located general store with the most modern techniques and medications. After a day on the road—usually within a 50-mile radius—Dr. Cannon's office hours would begin at 5:30 p.m. and stretch on until the last patient was attended to. His record-keeping sessions routinely filled the hour before midnight—rounding off Dr. Cannon's 18-hour day.

At all hours

But emergencies often interrupted his sleep. Dr. Cannon claimed his real office hours were 24 hours a day, and his patients revered him for it.

Dr. Cannon died in 1966 at the age of 68. He will be long remembered—most especially by the more than 5000 North Carolinians he helped bring into the world, some of them at the side of a rutted country road.

Reference: 1. Doctor in the bockwoods, in Lee RV, Eimerl S *et al*: *The Physician* New York, Life Science Library, Time Inc., 1967, pp. 38-50



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When the history reveals anxious depression...

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Limbitrol also has a rapid onset of action which may lead to greater patient compliance. In a multicenter study, patients taking Limbitrol experienced 62% of their overall improvement within the first week of therapy.[2]

In another multicenter study,[3] the following symptoms associated with anxious depression were significantly reduced during the first two weeks of therapy:

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- ☐ Early insomnia—91%
  Middle insomnia—87%
  Late insomnia—89%
- ☐ Gastrointestinal upset—73%

In two multicenter studies, only 1.9% of Limbitrol patients experienced cardiovascular side effects.[3]

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness such as operating machinery or driving a car.

References: 1. Rickels K: Drug treatment of anxiety, in *Psychopharmacology in the Practice of Medicine,* edited by Jarvik ME; New York, Appleton-Century-Crofts, 1977, p. 316. **2.** Feighner JP *et al: Psychopharmacology 61:* 217-229, Mar 1979. **3.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

In moderate depression and anxiety

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see summary of product information on following page.

LIMBITROL® TABLETS Ⓥ Tranquilizer—Antidepressant
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.
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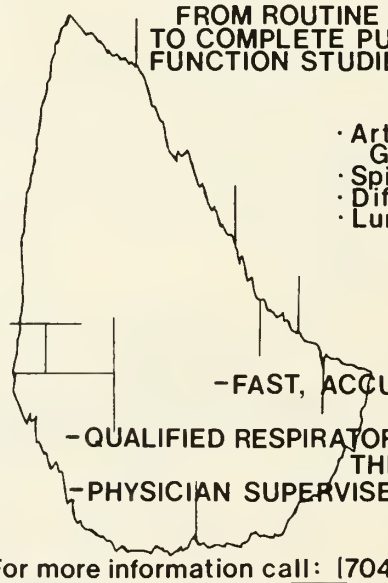
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The Practice of Family Medicine in North Carolina

James G. Jones, M.D., Dennis A. Revicki, Ph.D., and Marianna Tepaske

GENERAL and family physicians provide approximately one-third of the ambulatory medical care in the United States.[1] The specialty of family practice was established in late 1969. Today, a little more than a decade later, family practice is a discipline in evolution. In 1931, eighty-three percent of all private practitioners were family physicians. By 1979 they comprised only 18 percent of physicians delivering patient care.[2] In the 1970s there was a great proliferation of family practice residency programs resulting in a significant increase in the number of residency-trained family physicians practicing throughout the United States.

The medical practice characteristics and the delivery of medical services by family physicians are of considerable interest since the emerging practice patterns of young family physicians are likely to influence the future content of family practice.[3] Marsland,[4] Curry[5] and, more recently, Rosenblatt[6] have investigated the practice characteristics and medical care provided by family physicians. More than ten years ago the clinical content of general practice in North Carolina was investigated.[7] In this study, the similarities and differences between general practice and other primary care specialties were explored.

These studies were limited by the fact that there were few family practice residency programs in existence and there were only a small number of residency-trained family physicians in practice during the time the data were collected. Therefore, the impact of these physicians on the content and practice of family medicine could not be completely evaluated.

Investigations concerning the practice of family medicine are important. They provide information necessary for the development of residency program curriculum, characteristics of the ambulatory medical care provided by family physicians, and hospital credentialling of family physicians. The objective of the present study was to assess the medical practice activities of family physicians in North Carolina.

Methods

To assess the medical practice activities of family physicians in North Carolina, a 40 question interview schedule was developed. The first section contained items requesting information on general demographics, medical education and postgraduate training, and practice characteristics. The remaining sections included questions concerning medical care delivery, professional services, and patient population characteristics. The specific questions used in the interview schedule, in addition to those written by the authors, were derived from a number of sources including national and local studies of family practice.[8]

A modified version of the National Ambulatory Medical Care Survey Patient Record[9] was used to gather specific information regarding a subsample of 150 consecutive patient encounters in each physician's practice. These forms include information on date of service, patient demographic characteristics, reason for visit, medical diagnoses, diagnostic services provided, and the length and disposition of the encounter. The International Classification of Health Problems in Primary Care (second edition) was used to record up to four diagnoses per patient visit.[10]

In the spring of 1982, a random sample of the 552 diplomates of the American Board of Family Practice in North Carolina were mailed an invitation to participate in the study. The letter indicated that participation would require a brief interview and the reporting of 150 consecutive patient encounters during the days following the interview. Of the 200 invitation letters mailed out, 88 indicating a willingness to participate were returned, resulting in a response rate of 44 percent. Of these physicians, three were unable to participate in the study for various reasons. Eighty-five family physicians were interviewed and 80 supplied completed encounter forms.

Results

The low response rate raises some question concerning the representativeness of the sample. To evaluate this, the demographic, training and practice characteristics of the respondents in the study sample were compared with data obtained from the NCAFP and other published sources.[2, 11, 12] The distributions of characteristics in the comparisons were similar, suggesting that the physicians in the study sample were representative of the population of family physicians practicing in North Carolina. The demographic characteristics of the sample were comparable to similar statistics compiled from national studies of family physicians practicing in the Southeast.[11, 12]

Physician ages ranged from 30 to 68 years, with an average age of 42 years. Of the 85 physicians the majority were male (97%), white (96%), married (96%), and possessed two or more years of post-doctoral training (59%). The average year of graduation from medical school was 1965, with a range of 1941 to 1978.

From the Department of Family Medicine, East Carolina University School of Medicine, Greenville 27834.

Table 1
Practice Location

Community Population	Percentage
Greater than 40,000	16
25,001-40,000	18
10,001-25,000	21
5,000-10,000	21
Less than 5,000	25

In respect to medical practice characteristics, most of the respondents indicated that they were in solo (39%), partnership (22%), or single specialty group practice (25%). Only 13% were in multiple specialty group practices. Most physicians practiced in small cities or towns and rural areas with populations less than 25,000 (see table 1). More than 66% of the practices were located in these areas. Eighteen percent reported practicing in cities with populations between 25,001 and 40,000. The average number of years in practice was 14 for the group, with a range from 1 to 41 years. Significantly, the average number of years in practice at their current location was 12.8 years with a range from 1 to 36. It appears that most of the physicians sampled remained fairly stable in their practice location. The sample physicians reported working an average of 58 hours per week, ranging from 42 to 84 hours per week.

Information on the characteristics of hospitals and hospital privileges of the family physicians included in the study were requested. Ninety-four percent of the physicians were associated with hospitals where they admit patients. Number of hospital beds ranged from 20 to 400, with 59 percent between 100 and 399. For most of the physicians (70%), the hospital was nine or less miles away. About ten percent of the physicians reported that the closest hospital was more than 20 miles. Approximately 93 percent of the family physicians had active full-time hospital staff privileges.

Medical service delivery characteristics are summarized in table 2. An average of 145 patients per week are seen by the family physicians in the sample. Between 100 and 159 patients are seen per week by approximately 58 percent of the physicians. Most patient encounters occur in the office setting. Physicians reported spending an average of 13.8 hours in the hospital, 4.4 hours in the emergency room, and 3.1 hours in nursing homes. The average number of days between scheduling a nonemergency appointment and the actual appointment was about three days for established patients and four days for new patients. Most of the family physicians interviewed reported that they included pediatrics (95%), emergency care (97%), counseling (97%), and house calls (89%) as part of their medical practice. Approximately 51 percent of the physicians reported providing obstetric services to their patients.

Table 2
Medical Service Delivery

Patient Office Visits Per Week		Percentage
60-99		8.4
100-129		32.6
130-159		25.3
160-189		20.4
>190		13.3
Practice Settings	**Average Hours Per Week**	**(Range)**
Office	40.2	26-60
Hospital	13.8	2-30
Emergency room	4.4	1-25
Nursing home	3.1	2-30
Home	1.7	0-7
Other	3.1	0-8

Patient encounter information was requested from all physician offices. In total we received 8854 ambulatory patient encounter forms. Patient demographic characteristics for these encounters are summarized in table 3. Fifty-six percent of the ambulatory encounters are with females. The distribution of race in the sample encounters compares well with statewide distributions. Sixteen percent of family physician office encounters are with infants or children under 14 years of age. Twenty-two percent are with geriatric patients.

Continuity and comprehensiveness of care represent important precepts in the practice of family medicine. Results of the present study indicate that continuity of care is realized for a majority of patients. More than 88 percent of the patients had been seen previously by the physicians and 60 percent had been seen for the same diagnosis. The family physicians sampled provided the majority of care for 83 percent of the patients and 59 percent of these patients' families. Information regarding the patient's major reason for visit are summarized in table 4. Almost twice as many visits occurred for acute problems as for chronic problems. Fifteen percent of the visits were for non-illness care.

Information on various diagnostic services that may be ordered or provided during an office visit were reported. A limited history or examination was performed during 55 percent of all visits. The procedures provided most frequently were blood pressure checks (59%) and clinical laboratory tests (36%). A general history and comprehensive examination occurred during 16% of the visits.

The encounter diagnostic information was summarized using the diagnosis cluster methodology developed by Schneeweiss et al.[13] The ten most frequent diagnosis clus-

Table 3
Patient Characteristics for Office Encounters

	Percentage (N = 8854)
Sex	
Male	44
Female	56
Race	
White	81
Black	18
Other	1
Age	
<3	6
3-14	10
15-24	14
25-44	26
45-64	23
≥65	22

Table 4
Major Reason for Patient Visit

Reason	Percentage
Acute Problem	52
Chronic Problem	29
Post Surgery or Injury	2
Non-Illness Care	15
Other	2

ters abstracted from the office encounters are reported in table 5. These diagnosis groups account for approximately 53 percent of the collected ambulatory encounters. The most frequent medical problems treated by family physicians in the sample include acute upper respiratory tract infections, hypertension, diabetes mellitus, pre- and postnatal care, and soft tissue injuries. Eleven percent of office visits were for general medical examinations.

Discussion

This study was designed to assess the content and medical practice activities of family physicians in North Carolina. Several important conclusions can be drawn from the results of this study regarding the practice of family medicine in North Carolina.

Certain characteristics that typify the family physician in North Carolina are worth highlighting. The typical family physician is engaged in the delivery of comprehensive front line medical care. Children, women, and elderly patients seek the services of the family physician with great regularity, representing 16%, 56%, and 22%, respectively, of the family physician's ambulatory practice. Family physicians provide a significant portion of the health care for the women in North Carolina. The clinical content of family practice is broad and continues to demonstrate that family physicians serve the entire general population.[14, 15]

The results of this study indicate that family practice is not just an outpatient, ambulatory care specialty. Family physicians in the sample spent an average of 26 percent of their work time in hospital settings. This replicates the Rosenblatt et al. study[6] which found that on a national sample 23 percent of the family physicians' encounters occurred in the hospital setting.

There were some findings that might surprise other specialist colleagues. Ninety-seven percent of family physicians regularly include various types of counseling in the routine service they provide patients. Perhaps most surprising was that 89% of family physician respondents in North Carolina still routinely make house calls.

Table 5
Ten Most Frequent Diagnosis Clusters

Diagnosis Cluster	Rank	Frequency	Percent
General Medical Exam	1	1027	11.6
Acute URI	2	753	8.5
Hypertension	3	637	7.2
Diabetes Mellitus	4	425	4.8
Pre- and Postnatal Care	5	398	4.5
Soft Tissue Injuries	6	336	3.8
Acute LRI	7	319	3.6
Urinary Tract Infections	8	283	3.2
Depression Anxiety	9	266	3.0
Otitis Media	10	257	2.9
Total		4701	53.1

Of great significance is the apparent change in the direction of family physicians regarding the inclusion of obstetric service in the practice of family medicine. Fifty percent of family physicians in North Carolina surveyed in this study regularly provide obstetrical service to their patients. This is a radical shift in attitude by family physicians from fifteen to twenty years ago when as few as 15% of family physicians in North Carolina regularly delivered babies. This finding parallels recent national studies.[1, 6, 12]

Despite national trends for physicians to engage in group practices, North Carolina family physicians still often establish solo practices. The fact that about one in five family physicians in the state located in a rural area may suggest that the family physician is best prepared to practice in this setting. The physicians tend to remain in their practice locations for a long time.

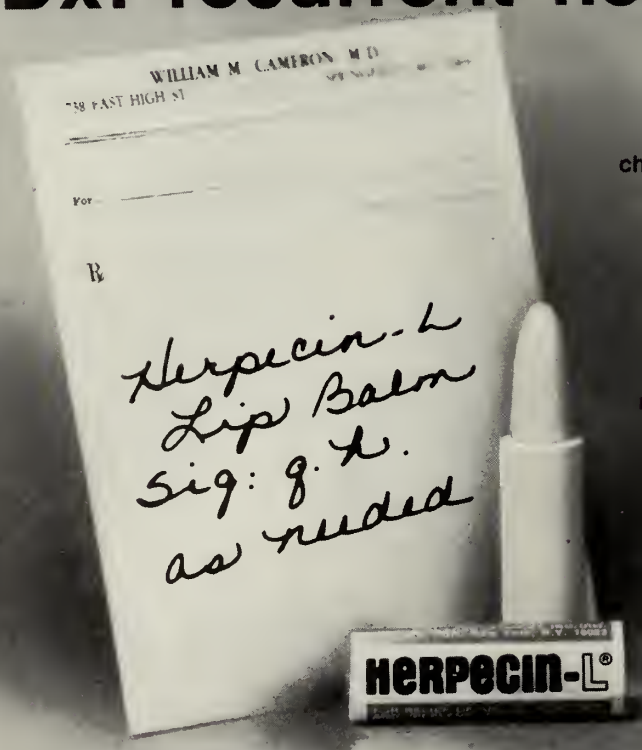
Finally, resident training programs need to be sensitive to the realities of the medical practice world.[6, 14, 15] There is evidence that family physicians provide services in a number of settings including the office, hospital, and nursing home, treat a broad spectrum of medical conditions, and serve the entire patient population from infants to geriatrics. The clinical content of family practice, as represented in this study, compares quite closely with the definitions and goals of the specialty, in particular for residency-trained family physicians. Regional differences were found in the national study[3, 6] and are validated in the present investigation. Resident education programs need to meet the requirements for particular regions, as well as train physicians to treat the entire general population for a broad spectrum of illnesses in both ambulatory and hospital settings. The impact of the new breed of family physician specialist is now beginning to affect health care delivery in North Carolina. Privileges on hospital medical staff clearly need to reflect these changes through credentials in areas of training and demonstrated competency.

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Bulletin Board

Genetic Clinics

For the past year, the Division of Health Services has been providing Genetic services to the citizens of the North Central Region of North Carolina. These services have, in part, been provided through quarterly satellite genetics clinics and include medical genetic evaluations, testing, counseling and follow-up to at-risk families. Risk factors may include:

—patients with known familial (genetic) disorders.
—individuals with multiple malformations or birth defects.
—individuals with a birth defect and a positive family history.
—couples or families interested in genetic counseling regarding risks of occurrence or recurrence of familial disorders or birth defects.
—women with a history of 3 or more spontaneous abortions.

A calendar of clinics has been scheduled for 1984. The dates are as follows:

Tuesday, March 13, 1984
Tuesday, June 5, 1984
Tuesday, September 25, 1984

Clinics are held at the Developmental Evaluation Center, 2311 W. Cone Blvd., Suite 143, Greensboro, N.C. Approximately six new families can be scheduled at this time. Appointments may be made by calling the DEC at (919) 282-1100 or by contacting Ms. Beverly Tenenholz, at the Division of Health Services in Winston-Salem, N.C. (919) 761-2390.

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February 19-22
"Beyond Advanced Clinical Teaching Skills"
Place: Rougemont
Credit: 20 hours Category I AMA
Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

February 20-22
"Selected Topics for the Practicing Clinician"
Place: Durham
Credit: 24 hours Category 1 AMA
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 24-26
"NCSIM/NC-ACP Joint Meeting"
Place: Greenville
Info: Kathy Adams, North Carolina Medical Society, Box 27167, Raleigh 27611. 919/833-3836

March 1-3
"2nd Annual Diving Accident Symposium"
Place: Durham
Credit: AMA, AAFP, ACEP
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 6
"Duke Tuesday"
Place: Durham
Credit: 5 hours Category I AMA
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

March 6-7
"The Least Restrictive Alternative: Programmatic and Management Issues"
Place: Raleigh
Info: 919/966-5463

March 7-10
"Internal Medicine: 1984"
Place: Chapel Hill
Credit: 25 hours Category 1 AMA
Fee: $250.00
Info: William B. Wood, M.D., 231 MacNider Bldg 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

March 15-16
"Eighth Annual Cancer Research Symposium"
Place: Chapel Hill
Credit: 11 hours Category 1 AMA
Info: Mrs. Mimi Minkoff, Cancer Research Center, UNC School of Medicine, Chapel Hill 27514. 919/966-3036

March 18-21
"Improving Residency Rotations: Curriculum Planning and Negotiation"
Place: Rougemont
Credit: 20 hours Catetory 1 AMA
Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

March 28-31
"Clinical Epidemiology"
Place: Chapel Hill
Credit: 24 hours
Info: Ruth De Bliek, 322 MacNider Bldg. 202H, UNC School of Medicine, Chapel Hill 27541. 919/966-3641

April 7
"13th Annual New Bern Symposium: Infections Disease"
Place: New Bern
Info: William B. Hunt, Jr., M.D., Box 2157, New Bern. 919/633-8607

April 8-11

"Administrative Skills: Faculty as Managers"
Place: Rougemont
Credit: 20 Hours Category 1 AMA
Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

April 10

"37th Annual Medical Symposium: Pulmonary Medicine"
Place: Greensboro
Info: L. S. Slotnick, M.D., 1018 North Elm Street, Greensboro 27401 919/275-7238

April 11-14

"3rd Annual Spring OB/GYN Symposium"
Place: Durham.
Credit: AMA, ACOG
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

April 12

"North Carolina Neuro-ophthalmology Review"
Place: Chapel Hill
Credit: 2.5 hours Category I AMA
Info: Baird S. Grimson, M.D., UNC School of Medicine, Chapel Hill 27514.

April 20-21

"Carolina Ocutome Workshop"
Place: Chapel Hill
Credit: 13 hours Category 1 AMA
Info: David E. Eifrig, M.D., UNC School of Medicine, Chapel Hill 27514.

April 25

"Current Concepts in Otolaryngology for Primary-Care Physicians"
Place: Chapel Hill
Fee: $50.00
Credit: 6 hours Category I AMA

April 27

"Biochemistry Symposium"
Place: Chapel Hill
Info: William B. Wood, M.D., 231 MacNider Bldg. 202H, UNC School of Medicine, Chapel Hill 27514 919/962-2118

OUT OF STATE

February 12-17

"Postgraduate Course in Diagnostic Imaging"
Place: Cancun, Mexico
Fee: $475
Credit: 25 hours Category 1 AMA
Info: Donald R. Kirks, M.D., Box 3834, Duke University Medical Center, Durham 27710. 919/681-2711, ext. 286 or 287

February 20-22

"Gold Coast Seminar: Surgery"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 22-25

"Medical Computing"
Place: Key Biscayne, FL
Credit: AMA, AAFP
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 4-10

"Sports Medicine"
Place: Snowshoe, WVA
Credit: 20 hours Category 1 AMA
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 5-7

"Gold Coast Seminar: Pediatrics"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 8-11

"New Horizons for Psychosomatic Medicine"
Place: Hilton Head, SC
Credit: 20 hours Category I AMA
Info: Joan K. Erpf. 316/379-0191

April 9-11

"Gold Coast Seminar: OB/GYN"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

Letters to the Editor

Herpes Zoster Ophthalmicus

To the Editor:

There is an ever-threatening and rising incidence of Herpes Zoster Ophthalmicus (shingles arising from infection of the gassarian ganglion in the middle fossa of the skull). Because of the seriousness of this formidable disease with its complications leading to blindness and trigeminal neuralgia (corneal damage, irido-cyclitis, retino-choroiditis, and optic nerve involvement, leading to atrophy), prompt diagnosis is of the utmost importance. This is particularly true when erythema and papular formation is seen on the tip of the nose or alongside the nose, indicating that the naso-ciliary branch of the ophthalmic division of the trigeminal nerve is involved, which indicates the impending involvement of the ocular structures in 100% of the cases.

Prompt therapy, such as steroids, Decadron, must be given at once in large doses and then tapered off over the next 5-7 days. This therapy eliminates the entire pathologic process within 48 to 72 hours.

Analgesics are given to relieve the pain for the first 24 hours but *no hospitalization* is necessary. Patients may return to work within 24 to 48 hours.

Milton J. Friewald, M.D.
2401 Pennsylvania Avenue
Philadelphia, PA 19130

Thorotrast

To the Editor:

In the September 1983 issue of the *NC Medical Journal* Drs. Merlo, Faulk, and Dudley presented and discussed a case of Thorotrast-induced hepatic malignancy. They suggest that serial abdominal radiographs are useful in surveillance of thorium-exposed patients;[1] however, this is not substantiated by objective data.

We are following a patient referred for evaluation thirty years after injection of Thorotrast for cerebral arteriography. She has asymptomatic thorium deposits in her liver and spleen; liver-spleen scan, blood counts, and serum chemistries are all within normal limits. A literature search revealed very little objective data on early detection of Thorotrast-induced malignancies. Despite extensive follow-up data and well documented increases in both malignant and non-malignant morbidity and mortality by the Japanese[2] and other national Thorotrast studies, there are no prospective studies attempting to establish predictors of these complications.

There have been several studies observing the prevalence of x-ray, serum chemistry, blood cell, and chromosome abnormalities, but these results have not been correlated with eventual outcome. Only Janower and associates[3] have prospectively examined exposed subjects with comparison to a control group. They found "apparent" differences in Bromsulphalein retention and alkaline phosphatase and a marked increase in the number of chromosome aberrations. Unfortunately, they had only thirty-four subjects, followed them for only three to four years, and did not correlate their findings with outcome.

A major reason for the absence of prospective studies may be best expressed by Oliveira and colleagues in their description of the experience in Portugal: "People injected with $Th^{0}2$ are aware they have a potential malignant condition (caused by medical treatment) and they avoid doctors and hospitals, refusing periodic clinical and laboratory examinations."[4] Intensive follow-up has been further discouraged by the absence of good therapy for most of the complications described. Despite a recent report of early detection and subsequent successful resection of a Thorotrast-induced cholangiocarcinoma,[5] there are no effective interventions for most of these patients.

Serial abdominal radiographs may be of use in follow-up of this group of patients; however, there is no literature support for this or other surveillance procedures. This is an excellent example of extensive epidemiologic data collection in identification and description of a problem; however, this has been of little aid to the practicing clinician in determining appropriate follow-up and surveillance of individuals at risk for these iatrogenic complications.

Bayard L. Powell, M.D.
Johnny B. Craig, M.D.
Bowman Gray School of Medicine
Winston-Salem, NC 27103

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Emergency Use of Epinephrine

To the Editor:

I would be very grateful if you could alert members of the North Carolina Medical Society to the following needs:

1. According to the North Carolina Board of Medical Examiners in excess of 1,500 non-physicians have been trained and licensed in accordance with 21 NCAC 321 this last year to administer epinephrine in the emergency situation of an adverse reaction to insect venom, drugs or foods. To be relicensed, these individuals must take a refresher training course annually.

2. There is a great need for physicians, especially allergists, to conduct these brief (½ hour) training courses to not only requalify those already in the program, but add to this pool trained non-physicians, who, like those trained in CPR, can administer life-saving aid when a physician is not immediately available.

3. I would be very glad to supply materials and any other

assistance to any physician wishing to devote a little time to this vital program. In addition, the State Office of Emergency Medical Services at the Department of Human Resources, PO Box 12200, Raleigh, NC, 27605-2200 can be contacted for regulations covering the program and for the necessary forms.

Claude A. Frazier, M.D.
Doctors Park
Asheville 28801

Problems with DRGs: A Letter to Dewey Dorsett, M.D., President of Metrolina Medical Peer Review Foundation, Inc.

Dear Dr. Dorsett:

I am writing to you on behalf of the medical staff of Lincoln County Hospital. At a recent meeting, the medical staff adopted the following resolution: "Be it resolved that the Professional Review Organization be requested to provide a PSRO staff physician consultant to be available by phone to provide consultation on admissions and with the power to authorize admission for those patients over whom they have hospital review authority when the attending physician is *in doubt* about PSRO approval."

This letter is being written to request that the Medical Peer Review Organization give serious consideration to the adoption of a physician consultant service in view of the continuing problems with review and approval of patient admission. The reasons for the practicality of such a physician consultant to act as a preadmission consultant and approval source follow.

1. A problem arises when an attending physician is in doubt about PSRO approval of an admission which the attending physician feels is needed. The attending physician needs to have the benefit of talking to a PSRO physician to obtain approval or disapproval.
2. It is assumed that the capacity of the PSRO to give retrospective review to admissions will increasingly work to disadvantage the attending physician (and of course the hospital and the patient) as the review is always made after the admission criteria have been satisfied by the attending physician, and as the review by a PSRO physician is always from a retrospective viewpoint. The provision of a preadmission consultation will provide that the consulting physician will always be involved at the level of the attending physician, which is from a prospective viewpoint.
3. It is felt that the implied and the explicit negative bias that increasingly enters the attending physician's decision-making to determine admission is brought about by the pressures of peer review and by PSRO's zeal to reduce admissions within their jurisdiction.
4. It is felt that increasingly the attending physician will and can make decisions that are detrimental to his or her own best judgment and to the patient's best care because of the overriding pressure of possible peer review disallowment of the admission.
5. There will undoubtedly develop in the near future cases in which problems will arise which are serious in that there can be a violation of someone's rights. They can give rise to malpractice cases and they can cause irreparable damage to the doctor-patient relationship. We feel it is important that the consulting PSRO physician be involved in this particular facet of the physician-patient relationship, as the pressures are now toward preventing the allowance of judgment errors that actually would be taken from the standpoint of the safety of the patient's health (e.g., errors on the side of safety), and of the physician's moral or judgmental, as well as legal, responsibilities.
6. We are aware that there have been, and will continue to be, instances wherein strongly held positions by the attending physician are overridden. Admissions or stays that have been denied are those involving cases of fever of undetermined origin, stroke, angina, syncope, and acute jaundice with accompanying illness. These are a few of the known examples when disallowment has occurred. At this institution patients have been disallowed admission or sent home early on the basis of alleged overstay, and within a matter of hours or days the patient was worse or dead.
7. It is known that there are variations in opinions by the reviewing physicians about the application of the criteria and standards of care of each case. In view of these human judgment errors or variances, as well as the opinions that are forthcoming from such situations, the physicians at Lincoln County Hospital feel that it is very important that the reviewing physicians be made available to participate in the prospective care judgments that the attending physician faces rather than benefit only from the safer retrospective judgments of which all attending physicians could benefit, if they were allowed to work only from that position in the care of their ill patients.

The Lincoln County Hospital medical staff feels very strongly about this concept, and feels it is important that the PSRO institute a workable plan that will fulfill the needs as outlined above. We further feel if private industry can provide preadmission consultation and authorization that is dealt with by a registered nurse (with an MD as back-up), that certainly something as important as this should be made equally available through the PSRO setting.

John R. Gamble, M.D.
Lincoln County Hospital
Lincolnton 28092

Containing Medical Care Costs

To the Editor:

"Doctor, if you don't mind, just go ahead and put me in the hospital to do those tests. My insurance will pay for it that way. I have been paying that company for 20 years. Now I am going to get my money's worth."

I offer an answer to Dr. Phillip's question #3 in his editorial page 770 in the December issue of the *Journal*. He asks, "How does one stop some doctors and hospital administrators from excessively using beds . . . especially when there is a strong financial incentive involved?"

The hypothetical patient's question above illustrates one situation in which the physician is in a difficult position to hold down medical care costs. In this situation the physician has basically two choices: 1. The physician makes the

patient happy and pads his own retirement fund by admitting the patient. 2. The physician stands fast as the vanguard of medical care costs, refuses to admit the patient, saves the insurance company $500.00, maintains his ethical standards, and loses $100.00 and the patient, who goes to Dr. Jones to be admitted.

There are many situations in which the choices are similar: the illness which could be treated at home if the patient and family were willing, the diagnostic problem which could be approached with maneuvers in a stepwise fashion versus a shotgun battery of tests, the patient who wants the extra lab or x-ray "just to be sure. My insurance will pay anyway."

I would prefer to believe that our professional ethics dictate decisions appropriate for good medical care of our patients regardless of the financial benefit to us. Observation tells me otherwise. It is unrealistic to give doctors the checkbook of our medical care account, reward them for spending the money, and then expect to control medical costs.

The answer lies in the patient's attitude. If the patient says, "Doctor, can't we treat him at home?" or "I want to be discharged as soon as possible," the physician will have the appropriate incentive to cut costs, when it is appropriate. Given the patient's urge to cut costs I submit that most physicians will do so when appropriate and only when appropriate.

Of course the patient must have some incentive himself. That incentive, of course, must be his own pocketbook.

Medical costs have been so effectively hidden from our patients that they see no relationship between their own medical insurance premiums and their use of medical facilities. Similarly in the "nonprivate" arena Medicaid conveys the "right" to medical care at convenience without restraint.

Patients must see a cost to themselves for each encounter with the medical system to supply an edge of restraint. The cost need not be large, and in the realm of Medicaid certainly should not be large enough to preclude medical care for a severe problem. The cost to the patient will be communicated to the physician and will be translated into restraint by the physician as he spends the patient's money.

A side effect of returning to a system closer to "pay as you go" is promotion of a more realistic view of the world. Currently our credit cards, checkbooks, and vast array of apparently free government services hide the fact that we all pay for what we get (though we are all convinced that we pay respectively more than our share). A healthier system in my view is one in which everyone is forced to see the cost and benefit of his actions at the time of his actions. Restraint is then internal and individual — much less expensive than an "agency" or "department" in charge of restraint — and less unsettling than the idea of an arm of government handing out or withholding medical care.

Cost containment incentive can be effectively directed at the physician. In prepaid medical care plans the physician is rewarded financially for frugality in the use of medical facilities. This is appropriate in my view only when the patient is similarly rewarded. An adversary relationship between doctor and patient is established when only the doctor has incentive to use the brakes. (Just such a system is in use in Blue Cross/Blue Shield's new "Personal Care Plan for the Piedmont.")

I am not sure how to accomplish a change in the direction I have described. Dialogue, certainly, is a start. I invite comments.

Evan A. Ballard, M.D.
Jonesville Family Medical Center
Jonesville 28642

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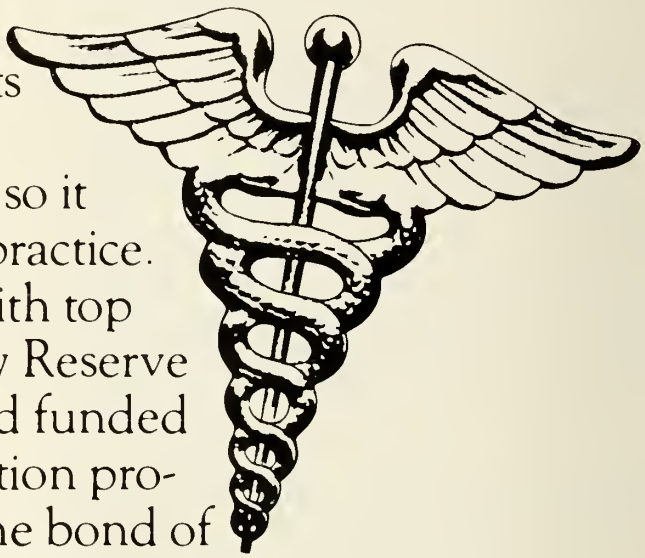
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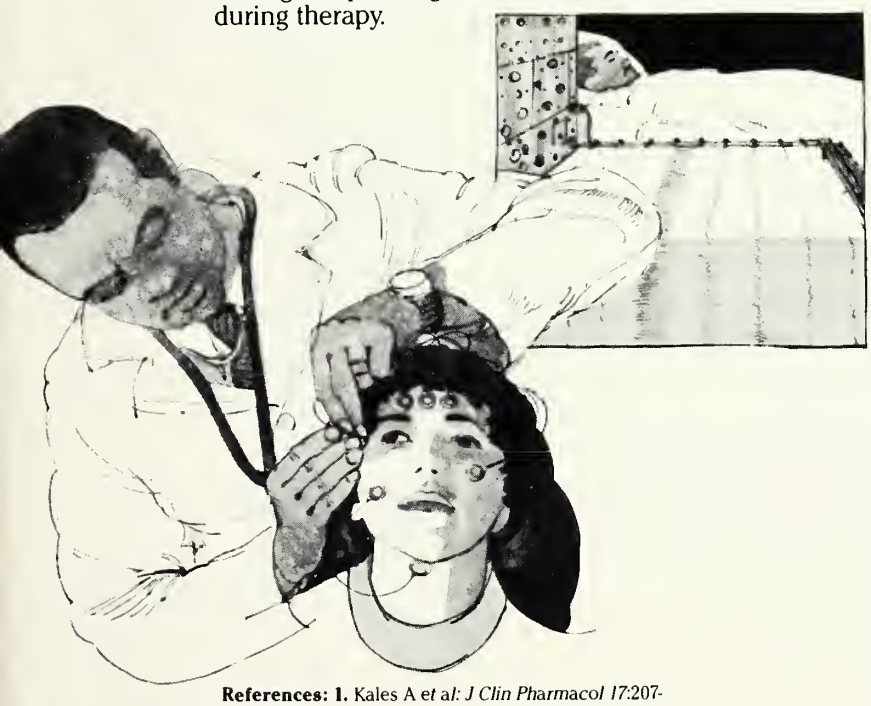
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North Carolina MEDICAL JOURNAL

for doctors and their patients

The Official Journal of the NORTH CAROLINA MEDICAL SOCIETY March 1984, Volume 45, No. 3

The Moses H. Cone Memorial Hospital

Much of this issue of the *North Carolina Medical Journal* has been written in Greensboro by physicians and staff members at Moses H. Cone Memorial Hospital and edited by Jack D. McCue, M.D.



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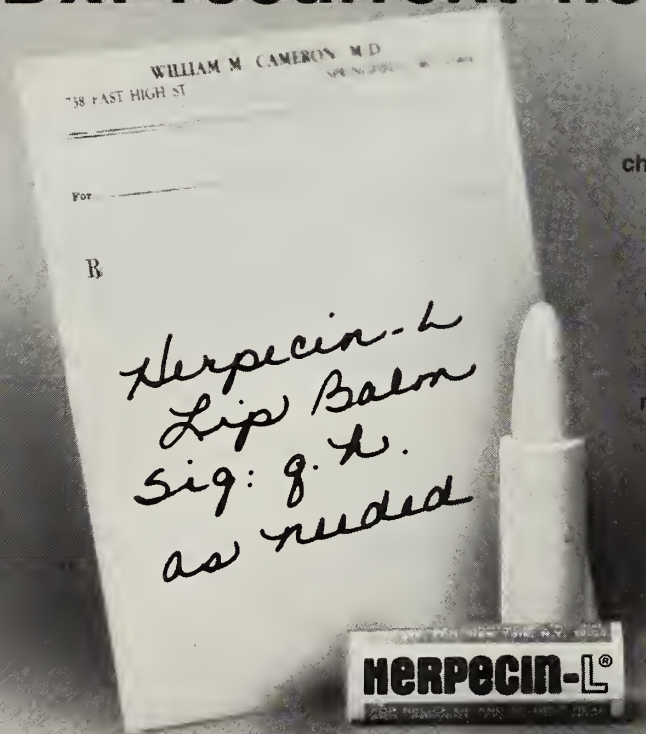
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Meetings Scheduled

Notice to: Delegates, Alternate Delegates, Officials of the North Carolina Medical Society, and Presidents and Secretaries of county medical societies.

Sessions of the HOUSE OF DELEGATES will convene in the Cardinal Ballroom, Pinehurst Hotel, Pinehurst, North Carolina, at the following times:

Thursday, May 3, 1984 — 10:00 a.m. — Opening Session
Saturday, May 5, 1984 — 2:00 p.m. — Second Session

A member of the CREDENTIALS COMMITTEE will be present at the Desk in the Hotel Lobby, Wednesday, May 2, 1984, 3:00 p.m. to 5 p.m., and Thursday, May 3, 1984, 8:30 a.m. to 10:00 a.m. to certify Delegates. Delegates are urged to bring their Credential Cards for presentation at the Registration Desk. Delegate Badges must be worn to be seated in the HOUSE OF DELEGATES.

REFERENCE COMMITTEE HEARINGS

Reference Committee hearings are scheduled to begin Thursday, May 3, 1984, at 2:00 p.m.

JACK HUGHES, M.D., President
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References:
1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

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II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina), PROCAROIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PRDCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCAROIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PRDCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PRDCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PRDCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents. (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCAROIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCAROIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PRDCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients; transient hypotension in about 5%; palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PRDCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PRDCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

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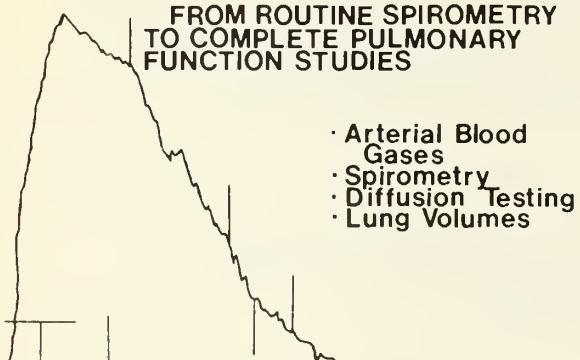
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SCIENTIFIC ARTICLE

The Beneficial Effect of a Phenytoin Loading Dose on Seizure Recurrence in Patients With Acute Repetitive Seizures: A Preliminary Report

Peter Gal, Pharm.D., Jack D. McCue, M.D., Michael Tate, B.S. and James Price, B.S.

PHENYTOIN is generally believed to be effective for the treatment of status epilepticus.[1-3] Recent studies usually recommend that a loading dose of 15-18 mg/kg be given intravenously to maintain serum phenytoin concentrations above 10 mg/L for 24 hours.[2-4] Physicians are reluctant to use doses of this magnitude (in excess of 1 g for a 70 kg person), however, despite the demonstrated safety of this dosage regimen if the infusion rate is kept below 50 mg/min.[2-5] Some of their reluctance may come from the lack of proof that loading doses reduce the frequency of seizure recurrence; our study addresses this question.

Method

Charts of patients 18 years of age or older, admitted to the Moses H. Cone Memorial Hospital from January 1979 through September 1983 with a diagnosis of seizure disorder were retrospectively reviewed. All patients included in the study (1) had an admission diagnosis of status epilepticus or several sequential generalized tonic-clonic or partial seizures; (2) were hospitalized for at least 48 hours; and (3) received phenytoin in the Emergency Room.

Information obtained included demographic patient data, seizure etiology, other anticonvulsants, and phenytoin doses. The physician and nursing progress notes were reviewed for any mention of seizure recurrence within 48 hours of admission, a period of time arbitrarily selected as the time for similar serum phenytoin concentrations to be achieved both in patients receiving an initial loading dose and in those begun on maintenance doses only. A loading dose was defined as an initial intravenous dose of 15 mg/kg or greater.

From the Moses H. Cone Memorial Hospital, 1200 N. Elm Street, Greensboro 27401-1020.

Results

Of the 55 cases included in the study (table 1), 41.2% of those patients not given an initial phenytoin loading dose had seizure recurrence within 48 hours compared with only 9.5% of those who received initial phenytoin doses of 15 mg/kg or higher ($p<0.06$). Of those patients with no previous phenytoin or subtherapeutic concentrations, 2/17 (12%) receiving a loading dose and 8/16 (50%) not receiving a loading dose had a seizure.

The etiologies for the seizures were comparable for the two groups of patients: they included alcohol-related (23), metabolic (4), brain damage (3), and unknown (25). The highest recurrence rate overall was among patients with alcohol-related seizures (26%). One patient had a hypotensive episode after receiving a loading dose.

Discussion

The findings from this retrospective study support the importance of initiating phenytoin therapy with a sizable loading dose (15 mg/kg or greater) in patients with status epilepticus or sequential seizures. While the need for adequate serum phenytoin concentrations is generally

Table I

Seizure recurrence in patients with various pre-seizure serum phenytoin concentrations who either received a phenytoin loading dose (>15 mg/kg) or did not receive a phenytoin loading dose.

	Loading Dose			No Loading Dose		
	#Pts.	#Seiz.	%Seiz.	#Pts.	#Seiz.	%Seiz.
No previous phenytoin	7	1	14	6	3	50
Subtherapeutic concentrations (<10 mg/ml)	10	1	10	10	5	50
Therapeutic concentrations	4	0	0	8	3	38
Toxic concentrations (>20 mg/ml)	0	0	0	6	1	17
Unknown	0	0	0	4	2	50
Total	21	2	9.5	34	14	41.2

accepted, the consequences of giving an insufficient initial bolus are not usually appreciated. Our results indicate that the risk of seizure recurrence considerably outweighs the potential risk of a large intravenous phenytoin dose. When appropriate precautions are taken, such as slowing the intravenous infusion rate to 10 to 25 mg/min in elderly patients, loading doses appear to be safe.

The most significant design limitation in this study is our reliance on seizure observation and documentation in the chart by nurses and physicians; we believe, however, that a clinical event as dramatic as a seizure is likely to be detected and recorded by most health care personnel. An expansion of the number of patients studied is needed, but the difference between the loaded and non-loaded groups is so large that the significant influence of phenytoin loading doses on seizure recurrence is likely to be further validated in a larger study.

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SCIENTIFIC ARTICLE

Affective Sickness and Normal Behavior

Arthur Freedman, M.D.

THE effort to improve the well-being of patients who are troubled by affective* disorders was for many years the most perplexing aspect of my practice. The language of psychiatry did not impart an adequate understanding of the processes involved, and the multiplicity of syndromes and the failure to distinguish consistently between qualitative and quantitative differences caused the classification of psychiatric diseases to be of only limited assistance. Nor was the assumption that psychiatric maladies resulted from unfavorable environmental situations altogether acceptable since so many people appeared to live through exceptionally trying experiences without ever having gotten sick at all. This latter observation has been affirmed in a review of the literature on this subject wherein the authors could not establish any clear relationship between stressful life events and psychiatric disease.[1]

The realization that patients could be interrogated without interference from psychiatric preconceptions was slow to materialize. It gradually became apparent, however, that the symptoms that constitute the core of almost all the nervous or psychiatric maladies seen in my practice are but few in number, that they are stereotyped and repetitious, and that they can readily be arranged into three discrete categories. These have been identified, in accordance with their central features, as morning fatigue, aberrations of mood and trust, and obsessive thinking and tension.

An astonishing number of people report, when they are asked, that they are more fatigued when they get up in the morning than they were when they went to bed the night before. Since this is before any energy has been expended, it is not unlike the after-effects of certain infections. Some people are tired all the time, some regain their vigor later in the day, and a few become fully productive by evening. If morning fatigue is their only complaint, they fall asleep without difficulty, but many of them awaken too early, and claim that this is why they are tired. On the other hand enough of them sleep through the night, with or without hypnotics, for loss of sleep not to be an adequate explanation for their fatigue. It is interesting that although loss of appetite is what is usually described, many of these patients are obese, possibly because they overeat in their search for energy. In the end, the feelings of fatigue and the desire to eat are determined not by magic but by the chemistry of the brain.

Mood and trust disturbances are altogether different. Mood disturbances include sadness, an urge to withdraw, a sense of futility which may extend to ideas of suicide, and in women a propensity for spontaneous crying. Loss of trust, which is often but not always a companion abnormality, refers to a loss of confidence in one's self or in others, coupled at times with ideas of reference, hallucinations, or a feeling of foreboding. Such annoyances intrude on patients' consciousness suddenly and without provocation in the same way that seizure activity does, persist for minutes or hours, and then, just as suddenly vanish, only to reappear after a longer or shorter interval in exactly the same form. Except for the few who say that they have no problems and therefore could not possibly have a nervous illness, virtually all patients ascribe their discomforts to unhappy events in their lives. Many claim, too, that they are able to throw off their discomforts at will; but careful inquiry always reveals that their spells begin and end spontaneously. In this sense the only people who appear to be adversely affected by environmental events are those who are susceptible as a manifestation of their affective maladies. Patients feel entirely "normal" between spells even when the interval between them is quite short. And after their well-being has been restored they no longer are troubled by their mood and trust difficulties, even though the situations which they claimed were responsible for them remain unchanged.

The third component of affective illness is obsessive thinking. This pertains to the insistent preoccupation of patients with events that take place in their lives, and with such reactions as discouragement (not depression), grief, shame, guilt, and so on, that accompany them. People who are obsessed with these problems are unable to fall asleep promptly, but this bears no relationship to the experience of fatigue the following morning. Tension, which commonly accompanies this symptom complex, is not only a subjective experience, but it may also be manifest objectively in such findings as hyperreflexia, sighing respirations, fluttering of closed eyelids, cold sweating of the extremities, anal spasm, and tenderness of the suboccipital, trapezius, and anal levator muscles, and of the costosternal articulations. The detection of these findings during an examination provides a clue to the presence of previously unsuspected affective illness.

Terms such as stress, depression, schizophrenia, anxiety, emotion, subconsciousness, and others of similar ambiguity have not been employed because their connotations are misleading, because there is no consensus as to their meaning, and because in some instances they imply only mystical notions.

Inasmuch as the symptoms that have been described are

* The dictionary says that affect relates to feelings and emotions and not to thoughts. But when the word is adopted by psychiatry, it must necessarily include both thoughts and attitudes. The word functional is not acceptable because most persons forget that function is dependent on structure.

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subjective, they cannot meet the present-day scientific requirement for documentation. Yet if they are perceived as the clinical manifestations of malfunctioning neurochemical processes, they may be regarded as finite, and this is how they are thought of by patients. Patients seem unable to communicate their discomforts in a straightforward manner; instead they almost always recount them in terms of what they believe to be the responsible causes.

The likelihood that the preceding descriptions accurately delineate discrete patterns of affective illness seems to be supported by the specificity of the clinical response of patients to selected medications. Three classes of drugs are effective: tricyclic compounds, in relatively small doses, rapidly abolish morning fatigue; thioridazine suspension (the least hazardous of the phenothiazines) eradicates mood and trust disorders, although less rapidly than the tricyclics dissipate fatigue; and minor tranquilizers ameliorate obsessive thinking and tension. These appear to act by slowing down the patient's gyroscopic mental activity, although they tend to aggravate mood disturbances should these happen to be present concurrently.

The well-being of patients has been improved with this regime quickly, safely, durably, often completely, and at relatively low cost. Patients have become able to perform up to their natural capabilities, and are no longer troubled by the situations they previously believed had provoked their malaise. Even though the maladies are in some instances cyclic, patients have fared better when their medications have been continued after their recovery, since relapses are common if the drugs are withdrawn. Compassion, although appealing, is not therapeutic; nor do people with affective disabilities seem to possess the ability to cope successfully. And since medications are administered as specifics, instead of as adjuvants to other forms of therapy, the treatment is not that of persons but rather of their neurochemical processes. Detailed personal histories are not needed; and when people do appear to be troubled by adverse circumstances, it is presumed that they have a predisposition toward affective types of illness.

These abnormalities are functional in that they are performance defects of organs and tissues. As such they are sufficiently distinctive to be considered as a nosologic entity, perhaps called affective brain syndrome. Manic states have been omitted because they are rarely encountered, as have the discomforts that are thought by many physicians as well as lay people to respond to counseling or placebos. Women are far more frequently affected than men, their complaints sometimes appearing in association with such events as menses, delivery, and menopause, which involve their reproductive systems. Media reports suggest that adolescents are more troubled than adults, but adolescents do not often seek medical attention for their difficulties. In the light of these observations, though, the influence of changes in hormonal patterns may be a relevant consideration.[2]

Abnormalities of affect are common in both general and specialty practices, but they are not always recognized. They occur as the sole disabilities of patients and also concurrently with illnesses which are conventionally called organic. Patients with these ailments do not always fare well, however, because of the professional compulsion to rule out structural changes in organs other than the brain. When the tests are normal the patients may be told that their symptoms are imaginary.

It has been my observation that when patients recover from affective ailments their symptoms, which previously had consisted of some combination of fatigue, mood and/or trust abnormality, obsessive thinking and tension, become replaced by qualities which are their approximate opposites. Ideally these are energy, aspiration, confidence and composure, although people do not often attain such an exalted state in full measure. Nevertheless, qualities like these can be only manifestations of something akin to normal neurochemical activity and therefore are also endogenous. The degree and hierarchy with which these qualities are expressed, on the other hand, are what make each individual unique.

The inference from the foregoing is that other fundamental characteristics of the mind are similarly inherent. These include the components of cognition, the aptitudes, the awareness of abstract concepts, and the values that quantitate the expression of each person's attributes. Behaviorists hold that the primary determinants of people's conduct are in the cultural environment, but it seems instead that the environment contributes content to qualities that in essence are inherent. This point of view also accounts for the variations in beliefs and practices that are encountered in different regions. The statistical studies of social scientists confuse this subject because they emphasize the homogeneous aspects of attitudes and behavior, but such studies actually measure only the molding effect of community pressures. If it is correct that neurochemical activity is the significant factor in the determination of behavior, then identification of the qualities by which it becomes manifest is a suitable subject for systematic study.

If the disorders of affect are viewed as abnormalities of neurochemical systems, they can be described with precision and treated with specifically acting medications. Since the symptoms of these disorders are perceived as the manifestations of endogenous processes, their opposites, the attributes of normality, must likewise be endogenous. The qualities that determine people's everyday behavior are therefore also inherent, and their modification by the cultural environment must be considered to be a supplementary contribution.

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SCIENTIFIC ARTICLE

Hearing Screening in "High Risk" Infants

Henry R. Boer, M.D., M.P.H.

THE exact number of infants born with significant hearing problems is uncertain, but estimates range from 1:700-1,000 in the normal term newborn[1-3] to 1:50-60 in the prematurely born infant or the infant sick enough to be admitted to a Neonatal Intensive Care Unit (NICU).[3-5] Hearing is essential for the normal development of language and speech, and impairment of hearing may influence psychological adjustment of the normal developing child. To enhance appropriate management and early rehabilitation of infants with deafness, the optimum time for identifying infants at risk is early in life.

Since 1982 all infants admitted to the Moses Cone Hospital NICU have been screened for hearing deficits before discharge. This report deals with a subgroup of those infants with a birth weight less than 1,500 grams.

Materials and Method

The study population includes premature infants admitted to our NICU from February 1, 1982 through July 31, 1983. Thirty-eight infants had birth weights of less than 1,000 grams: of these, 15 were tested, 3 were transferred to other institutions, and 20 died. Fifty-two infants were admitted with a birth weight between 1,000 and 1,500 grams. Forty-nine of these infants were tested, 2 were transferred and 1 died. Infants were tested using the Crib-O-Gram[6] a few days before discharge from the hospital when they were assumed to have no medical problems. The apparatus consists of a motion-sensitive transducer attached to the undersurface of the infant's bassinet which detects movements of the infant in response to a sound stimulus presented at scheduled intervals. A score of 50 or above was considered a "pass." Infants who failed the test were retested on two subsequent occasions. Infants who failed all three tests were studied further with brain stem evoked potential.

Results and Discussion

In 1973 a joint committee on infant hearing screening, with representatives from the American Speech and Hearing Association, the American Academy of Pediatrics, and the American Academy of Ophthalmology and Otorhinolaryngology cited five factors most often associated with hearing impairment in infants.[7] These factors were affected families; congenital rubella; defects of ear, nose and throat; bilirubin levels in excess of 20 mg/dl; and birth weight less than 1,500 grams. Studies by Feinmesser[2] and Simmons et al[8] have shown that additional factors such as maternal bleeding, difficult delivery, a 5 minute Apgar score less than 6, neonatal respiratory distress, sepsis and bilirubin level greater than 12 mg/dl also should be considered high risk factors. Of these, the most important are complicated deliveries and low Apgar scores.

Infants with similar birth weights were grouped and several factors commonly associated with hearing defects were analyzed.* In these weight categories, there were no babies with facial abnormalities, intrauterine infection, or a family history of deafness.

(1) Hypoxia. Hypoxia causes a loss of cochlear nuclei,[9] and Kileny et al[10] found statistically significant differences in auditory brain stem responses when they compared asphyxiated neonates with a group of healthy newborns who were matched for gestational age and weight. Anagnostakis et al[11] found that 8 of the 9 children with hearing damage in a group of 98 survivors of infants with a mean birth weight of 1,540 grams had suffered from apneic spells during the neonatal period. I looked at factors that might be associated with perinatal oxygen deprivation. Several babies had low 5 minute Apgar scores or required high percentages of oxygen and respiratory support; most of them weighed less than 1,000 grams. All babies weighing less than 1,000 grams, in fact, had repeated episodes of low pO_2 values on arterial blood gas analysis — potentially significant hypoxic insults. None, however, failed the Crib-O-Gram.

In our institution, we treat apnea vigorously with theophylline. Our protocol calls for the use of theophylline when the baby has three apneic spells that last longer than 20 seconds in any given 24 hour period. Serum theophylline levels are followed and theophylline treatment is discontinued gradually after an infant has been free of any apneic or periodic breathing spells for 3 days. Aggressive treatment with theophylline was probably responsible, I believe, for the absence of deafness in these high risk babies.

(2) Hyperbilirubinemia. In babies with neonatal hyperbilirubinemia, deposition of bile pigments may be found in the basal nuclei, including the cochlear nuclei.[12] All but two of our infants had bilirubin levels less than 12 mg/dl, and most of them had levels well below 10 mg/dl. In our institution, hyperbilirubinemia in prematurely born infants is treated with phototherapy at levels of 6 mg/dl, making severe hyperbilirubinemia uncommon. This is, I believe, responsible for the absence of deafness in our hyperbilirubinemic babies.

(3) Aminoglycosides. The role of aminoglycosides in the pathogenesis of hearing deficits is still not clear. Barr,[14] in a review, found few cases of ototoxic effects of aminoglycosides even after prolonged therapy during pregnancy.

From 3036 Lake Forest Drive, Greensboro 27408.

* Complete tables with weight categories and risk factors may be obtained from the author.

Other investigators found no evidence of ototoxicity in low birth weight infants.[11, 15] Our small infants often had, as expected, repeated doses and prolonged courses of gentamicin treatment. None, however, failed the test.

(4) Low Birth Weight. Mencher et al,[16] reviewing many factors that may influence hearing testing in newborns, concluded that the most effective remaining method for examining newborns' hearing is some form of observable change in behavioral activity associated with an auditory stimulus. None of the 64 babies with a birth weight less than 1,500 grams failed the Crib-O-Gram; two had to be tested three times, but passed with scores well above 50 on the third attempt.

Summary

There is no reason to believe that our babies are different from those commonly encountered in the neonatal units across the U.S.A. All were premature, many had perinatal complications, and several had low Apgar scores and repeated hypoxic insults. Our vigorous treatment of hyperbilirubinemia and extensive use of theophylline in the prevention and/or treatment of apnea, however, may be different from practices in other neonatal units. It may well be that this is, in large part, the reason I did not find hearing deficits in our study population.

All the premature infants are followed up in our High Risk Clinic where they receive developmental assessments at regular intervals. None of the infants was subsequently found to be deaf. It is too early, however, to know if they have the same perception for subtleties of sound, e.g., music appreciation, as the term infant not exposed to these risk factors. Screening of high risk infants for deafness is important so hearing impairment and deafness can be treated promptly.

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SCIENTIFIC ARTICLE

Heparin-Induced Thrombosis

William B. Herring, M.D. and Palmer F. Shelburne, M.D.

THROMBOCYTOPENIA following treatment with heparin has been recognized for many years, but heparin-induced thrombosis is less well-known despite the many reports of its occurrence since 1958. Its potentially serious consequences make it imperative that it be watched for in all patients on sustained heparin treatment. We recently encountered this complication of heparin therapy in a patient whose clinical course follows.

A 60-year-old man sustained an abrasion of his right leg while climbing steps. Healing was slow but there were no local signs of infection. Three weeks later he developed fever, sweating, and shaking chills. Fever to 103°F persisted without response to penicillin or erythromycin. He then had chest pain on deep inspiration but no cough, and was admitted to another hospital.

Thorough investigation for the cause of fever failed to yield a secure diagnosis. The chest X-ray on admission was normal, but by the fourth hospital day he had developed S_3 and S_4 heart sounds, cardiomegaly, pulmonary vascular congestion, and bilateral pleural effusions. There was sinus tachycardia with rates up to 150/min and ECGs showed left bundle branch block. Creatine kinase and lactate dehydrogenase isoenzymes were non-diagnostic. There was no evidence of volume overload. With vigorous treatment for congestive heart failure he improved and by the twentieth hospital day the chest X-ray had returned to normal. He had been afebrile since the ninth hospital day. On the thirtieth hospital day a radionuclide study showed symmetrical reduction of left ventricular contractility with a low ejection fraction of 36%. Acute myocarditis, probably of viral origin, was suspected but throat and rectal swab cultures for coxsackie- and echoviruses were negative, and acute and convalescent phase serum antiviral antibody titers were non-diagnostic.

A lung scan on admission showed perfusion defects in the left mid- and lower lung fields. Since the admission chest X-ray was normal these findings were thought indicative of pulmonary embolism. The arterial PO_2 was 69 mm Hg on room air. Other laboratory studies were normal, including a platelet count of 428,000/μl, prothrombin time of 12.5/11.0 sec, and activated partial thromboplastin time of 25/26 sec. Streptokinase, 250,000 u initially, then 100,000 u/hr for 24 hours was given IV, and then a continuous infusion of heparin was started. On the 15th hospital day, after treatment with heparin for 12 days at an average daily dose of about 50,000 u and an average aPTT of 52.4 sec (control 26.8 sec), his right foot and leg became numb, pale, and cold to the mid-calf. The platelet count was 40,000/μl (figure 1). A right femoral embolectomy was performed, yielding about 10 cm of organized gray thrombus and a small amount of fresh clot. Heparin therapy was stopped for about 8 hours and was resumed postoperatively at an initial rate of 800 u/hr (19,200 u/day). The platelet count rose gradually over the ensuing 4 days to 179,000/μl. The heparin infusion rate was gradually increased to 1800 u/hr (43,200 u/day) but the aPTT did not exceed 41.5 sec. On the 5th day after resumption of the heparin infusion the platelet count dropped to 74,000/μl (figure 1). The patient developed pain and signs of ischemia in the left foot and leg. Aorto-femoral angiography revealed multiple adherent thrombi in the aortic arch, the descending thoracic and supra-renal abdominal aorta, and the left common iliac artery. There were also filling defects in both common femoral, left superficial femoral, left anterior and posterior tibial, and right peroneal arteries (figure 2). Bilateral iliofemoral and infra-renal aortic thrombectomy was attempted but the Fogarty catheter would not traverse the iliac arteries. There was excellent inflow. Multiple passes with Fogarty catheters distally to the ankle level failed to yield thrombus.

Heparin was discontinued and anticoagulation was achieved with coumadin. The platelet count rose to 426,000/μl by the 5th postoperative day and the patient recovered without further complications.

Discussion

The temporal relationships among heparin therapy, thrombocytopenia, and signs of vascular obstruction constitute evidence that heparin given as treatment for pulmonary embolism caused this patient's thrombocytopenia and thrombosis, although confirmatory ex vivo studies were not done. The recurrence of thrombocytopenia and massive thrombi upon retreatment with heparin is virtually conclusive.

Thrombocytopenia commonly follows heparin administration by continuous or intermittent intravenous or by subcutaneous routes. There are at least two types.[1, 2] One occurs within 2 to 4 days after heparin treatment is begun, is mild and transient, and may resolve even if heparin is continued. The other is delayed, with more severe thrombocytopenia beginning usually after 6-13 days of heparin treatment (mean 9.8 ± 3.7 days, median 10 days) and reaching a nadir at 7-14 days. Mean nadir platelet counts were 29,000/μl and were as low as 5,000/μl.[3] Withdrawal of heparin is followed by return of the platelet count to normal within a median time of 4 days (mean 5.6 ± 5 days). Readministration of heparin causes a prompt recurrence of thrombocytopenia.

The incidence of heparin-induced thrombocytopenia has not been clearly determined. In prospective studies with

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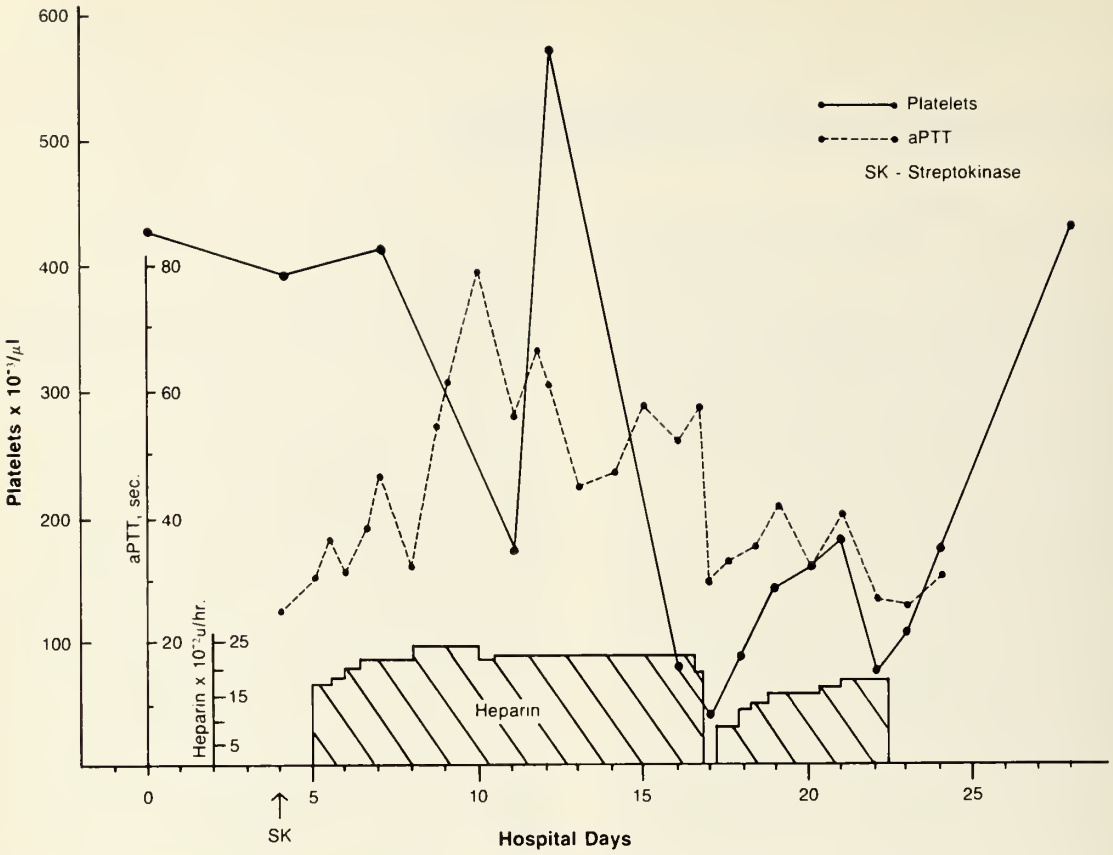


Figure 1. *Relationships among platelet count, aPTT value, and heparin dose during the hospital stay of the patient.*

monitoring by alternate-day platelet counts Bell and Royall, using bovine lung heparin, reported an incidence of 26% but only 7% when the heparin was of porcine gut origin,[4] whereas Powers et al, using porcine gut heparin, found it to occur in only 3% of patients.[5] The combined incidence from six prospective studies of patients treated with porcine gut heparin was 3.7%.[2] At the Moses H. Cone Memorial Hospital we have detected thrombocytopenia in one of 386 patients (0.3%) treated with beef lung heparin and in one of 256 (0.4%) treated with porcine gut heparin. Our true incidence may have been higher since our data were collected retrospectively and platelet counts were not routinely performed. Another factor contributing to a low incidence could be the generally short duration of treatment with heparin in our hospital (mean 6.0 ± 5.9 days, median 8 days).

Mechanisms

The mechanism of the early, transient form of thrombocytopenia is uncertain. Heparin may promote platelet aggregation by several mechanisms, including inhibition of platelet adenylate cylase.[2] The consequent reduction of cyclic AMP releases the arachidonic acid pathway from inhibition, resulting in the release from platelets of thromboxane A_2, a potent aggregant. Heparin also antagonizes the inhibitory effect of endothelial prostacyclin on platelet aggregation. Presumably platelet aggregation thus induced does not progress beyond the first phase, since it seems to be reversible. Thrombocytopenia is due to transient sequestration of large numbers of platelets.[1] Our patient may have shown this phenomenon since his platelet count dropped from 413,000/μl on the second day of heparin treatment to 173,000/μl on the sixth day, followed by an abrupt rise before thrombocytopenia was noted on the eleventh day. Alternatively, the platelet count of 573,000/μl could have been erroneous (figure 1).

There is abundant evidence that the later-appearing, more severe form of thrombocytopenia is mediated by a heparin-dependent antibody to a component of platelet membrane.[2, 3, 6, 7] The antibody is usually IgG but an IgM antibody has been described.[7] The platelet-IgG-heparin interaction that causes aggregation may require complement.[8] Aggregation of large numbers of platelets accounts for the thrombocytopenia. Platelet production is presumably uninhibited since bone marrow examination shows a normal or increased number of megakaryocytes.[1]

Using a variety of methods for their detection, heparin-dependent antibodies could be demonstrated in only 72% of 71 patients with heparin-induced thrombocytopenia in 14 studies.[2] The most widely used technique is observation of platelet aggregation upon the addition of heparin to the patient's platelet-rich plasma, or to normal platelets suspended in the patient's serum, with appropriate controls. Since the antibody is predominantly platelet-bound, residual circulating antibody levels in thrombocytopenic patients would reasonably be low, although the concentra-

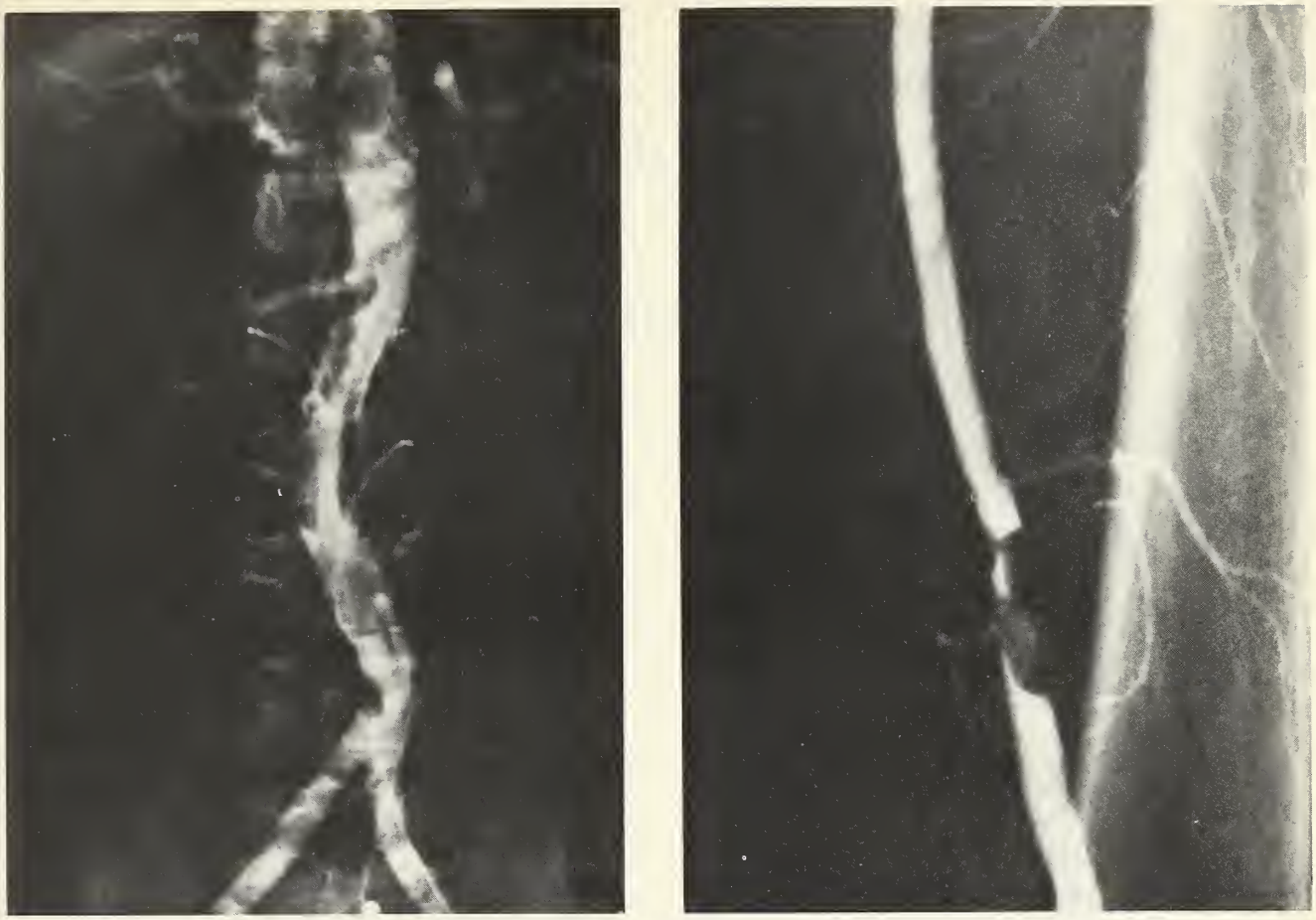


Figure 2. *Angiograms showing filling defects in the abdominal aorta (left) and left popliteal artery (right).*

tions of IgG and complement per platelet were found to be highest during thrombocytopenia.[7] The removal of large amounts of antibody from the circulation by platelet aggregation, possibly of the most highly sensitized platelets, might account for the high frequency of negative tests.

Most evidence favors a lack of dependence of the reaction upon the dose of heparin or upon the route or mode of administration.[2] Cines et al, however, showed a relationship to dose in the amount of C_3 deposited on normal platelets by the plasma of two patients with heparin-induced thrombosis.[8]

The duration of the thrombocytopenic response to heparin is not well-established. Rhodes et al found it present up to 2 months after recovery from heparin-induced thrombocytopenia in two patients, but absent in a third at 4 months.[7]

Clinical Manifestations

Heparin-dependent antibody-mediated platelet aggregation of sufficient magnitude to cause thrombocytopenia is followed by clinical manifestations of vascular obstruction in a high proportion of cases. In 17 prospective studies reviewed by Carreras that totaled 73 patients there were 45 instances of thrombosis (62%). In vessels with high flow rates (arteries) the thrombi are composed predominantly of platelets and fibrin, with few leukocytes and rare red cells. This has been called the "white clot syndrome."[9] While most often causing arterial thrombosis, commonly of large vessels, heparin may also induce clotting in the venous circulation, sometimes with pulmonary embolism.[3, 7] Other manifestations of heparin-induced thrombosis are myocardial infarction,[7] vein graft occlusion,[9] skin necrosis,[10] stroke,[3] and disseminated intravascular coagulation.[11] Surgical intervention is often required for thrombectomy or amputation.[3] If recognition and cessation of heparin administration are timely, recovery usually follows, depending upon the nature of associated conditions,[3] but outcomes may be fatal.[7, 10, 12]

Thrombosis may occur without absolute thrombocytopenia, but the fall in platelet counts remains consistent with aggregation of large numbers of platelets.[13] This emphasizes the importance of a baseline platelet count prior to starting heparin treatment.

Bleeding may occur from heparin-induced thrombocytopenia, with or without clinical evidence of thrombosis, but is less common than thrombosis. Carreras' review suggests an incidence of 22% (16 of 73). At least six patients who bled also had evidence of thrombosis.[2]

Thrombocytopenia occurring during heparin treatment is an indication for prompt withdrawal of heparin and anticoagulation, if necessary, with alternative drugs, usually coumadin. Aspirin and other antiplatelet agents have not been systematically evaluated for their ability to correct or

prevent heparin-induced thrombocytopenia or thrombosis, but aspirin has been shown to inhibit heparin-induced platelet aggregation in the platelet-rich plasma of a patient with a heparin-dependent antibody.[2] The effect of low-molecular-weight dextran[9] is difficult to evaluate, since rapid recovery after withdrawal of heparin is the rule.

Heparin resistance has been noted in patients with heparin-induced thrombocytopenia.[1] It has been attributed to release of platelet factor 4, a heparin-neutralizing factor, from the stimulated platelets. It could also be due to depletion of antithrombin III consequent to heparin-induced coagulation, or to the thrombotic event for which heparin was administered, due to consumption of antithrombin III by irreversible binding to activated clotting factors. Since heparin accelerates this process, reduced antithrombin III levels may be seen in any patient given heparin, intermittently or continuously, for more than a few days. Antithrombin III deficiency may be acquired in a variety of other conditions by impaired synthesis (e.g., liver disease, diabetes) or by excessive loss (e.g., nephrotic syndrome). Drugs other than heparin (e.g., estrogens) may lower the antithrombin III activity of plasma. Antithrombin III deficiency may also be hereditary.[14] Heparin resistance was present in our patient during re-administration of heparin, since with increasing doses to 1800 u/hr the aPTT failed to rise above 41.5 sec (figure 1).

Why, rather than remaining low, our patient's platelet count continued to rise for 4 days during the second period of continuous heparin infusion, albeit at lower doses (figure 1), is unclear. No drugs with known anti-aggregant properties were given during this period. Measurement of antibody and complement levels might have helped clarify this question.

When thrombocytopenia appears in a patient beyond the fourth day of heparin treatment, regardless of route of administration or dose, the presence of a heparin-dependent antiplatelet antibody should be suspected. Platelet aggregometry may confirm but not exclude the diagnosis. Thrombosis should be suspected if signs of vascular insufficiency are present. Doppler testing and/or angiography may be useful. Vague pain in the low back and thighs and abdominal pain and distention have been observed one or two days prior to clinically evident vascular obstruction. These symptoms may be of ischemic origin, due to small vessel occlusion, and a helpful warning of impending larger vessel thrombosis.[2]

Heparin-induced thrombosis should be preventable in most cases by monitoring of platelet counts and by awareness of the possible significance of vague pains and heparin resistance. We have modified our heparin treatment protocol to include routine platelet counts prior to administration of heparin and on alternate days after the fourth day of continuous treatment, and an antithrombin III level upon evidence of a requirement for increasing doses of heparin to maintain prolongation of the aPTT.

Acknowledgements

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Medical Education at the Moses H. Cone Memorial Hospital: A Brief History and Comment

William B. Herring, M.D.

THE Moses H. Cone Memorial Hospital is a legacy from the estate of Mrs. Bertha Lindau Cone, who died in 1947, given in memory of her husband, a co-founder of Cone Mills, now one of the world's largest manufacturers of textiles. From its opening in 1953 the Hospital has had a significant commitment to medical education. Between 1954 and 1967 rotating internships, up to 10 per year, were offered under the voluntary part-time supervision of members of the medical staff.

After a decade of vicissitudinous experience with the rotating internship, the medical staff and trustees of the Hospital concluded that affiliation with a medical school offered the best prospects for a successful program in medical education. The University of North Carolina School of Medicine was approached and, after the favorable outcome of a thorough feasibility study, an affiliation agreement was concluded in November 1966. The famous Millis Report[1] was published that same year and the Coggeshall Report[2] the year before; they advocated in-depth training for primary medical care in continuity with undergraduate medical education, i.e., abolition of the free-standing internship. This initial affiliation agreement embraced these recommendations, but gave equal weight to two other major aims; they were to provide a community hospital-based clinical experience for medical students who might as a result be attracted to a career in primary care practice, and to develop a structure for effective continuing education of the medical staff.

To implement the affiliation, one full-time hospital-based faculty member each in internal medicine and pediatrics was appointed by the departments of internal medicine and pediatrics of the School. As evidence of the School's commitment it was decided that these should be tenure-track appointments, fully salaried by the School. To insure the teaching services a voice in the conduct of medical staff affairs these faculty were seated on the Medical Board of the Hospital.

Immediately there began a steady flow of fourth-year medical students for acting internships in internal medicine and pediatrics. In the early years, substantial numbers of students from schools other than UNC came to Moses Cone for accredited clinical rotations but later, upon the expansion of class size, available positions became limited to UNC students. Eventually clinical clerkships in internal medicine for third-year students and a few subspecialty rotations were offered and have been generally filled. Part of the second-year introduction to clinical medicine has been taught by full-time and clinical faculty for many years.

The Medical and Pediatric Teaching Services jointly developed a residency program in family medicine, which was among 16 programs that were approved at the first sitting of the Residency Review Committee for Family Practice on February 16, 1969. Our first residents were appointed in July 1969. This program flourished, but it soon became apparent that residencies in general internal medicine and pediatrics were needed, both to afford primary care training in these fields and to strengthen by interaction the family practice program. These were added in 1972 and steadily improved in quality as they grew in size. For about five years all three programs have been stable in size with most positions filled. Presently there are at each year-level of the three-year programs four positions in internal medicine, four in pediatrics, and six in family medicine, for a total of forty-two primary care residency positions.

In addition to the primary care residency programs there are or have been at various times a small number of residents at advanced levels rotating through obstetrics-gynecology, orthopedics, psychiatry, and some of the medical specialties. For many years there have been advanced trainees in anatomic and clinical pathology. This program was recently replaced by fellowships in dermal pathology and hematopathology.

Faculty growth has been commensurate with the increased numbers of students and residents. Since 1973 the full-time faculty has grown from one each in internal medicine and pediatrics to five in internal medicine, four in pediatrics, and three in family medicine. Nine are tenure-track; three are full-time or part-time clinical faculty. Also, the Hospital has hired two full-time hospital-based neonatologists for whom teaching is an integral function. There are part-time faculty in obstetrics-gynecology, psychiatry, and clinical psychology.

A large number of medical staff members, representing all specialties, make vitally important contributions to the teaching program and collectively comprise a large volunteer faculty. Their participation not only represents an essential augmentation of the faculty, for it is equivalent to several full-time positions, but also benefits students and

From the Moses H. Cone Memorial Hospital, Greensboro 27401-1020.

house staff by contact with highly skilled practitioners in all clinical disciplines. The contributions of the members of the Hospital's departments of pathology, radiology, and emergency medicine deserve special mention.

Residents entering the clinical training programs of the Moses Cone Hospital have come from 26 states and 41 medical schools. Since 1971 about 100 have completed their training and entered practice, two-thirds in North Carolina and the remainder in 20 other states. Although emphasis has been on preparation for primary care practice, about half those who have completed residencies in internal medicine have sought and secured fellowships in subspecialties of internal medicine.

The advent of the North Carolina Area Health Education Centers program in 1972 brought a new impetus and major changes in perspective to medical education at Moses Cone. The Hospital became an AHEC in 1974 and was charged with responsibility for health manpower development and continuing education compatible with the needs of a six-county area that includes Guilford, Rockingham, Caswell, Alamance, Randolph, and Montgomery counties. While the Greensboro AHEC has made important contributions in nursing, technology, and other medical support fields, the majority of its resources have been expended in graduate medical education at Moses Cone and in continuing education for practicing physicians in the area. Through the AHEC, the University of North Carolina is now the main source of funding for medical education at Moses Cone.

Initially, the teaching programs were handicapped by inadequate facilities. Office space had been converted from waiting areas, and conference rooms and visual aids were severely limited. Outpatient teaching had been conducted in the Guilford County Health Department building and organized around clinics operated by the Health Department. In January of 1970, when North Carolina began to participate in the Medicaid program, the Moses Cone Hospital medical staff accepted responsibility for operating those County-sponsored clinics deemed essential to the teaching programs. Medical staff physicians joined the small full-time faculty in providing services to County-sponsored patients and teaching of students and house staff. Guilford County rendered valuable financial and staff support and has continued its contributions in exchange for services rendered patients who qualify for county sponsorship.

In 1978 the first phase of the Hospital's building and renovation program was completed, including an outpatient department and a spacious library with comprehensive resources. The educational components were funded by the University through the Greensboro AHEC, but for several reasons some compromises were necessary, requiring that space intended for patient care be modified and used temporarily for AHEC staff and faculty offices. The next phase of the Hospital's construction program is nearing completion and will provide, among other facilities, definitive educational space and a short-term rehabilitation unit, unique for our state. These new accommodations should enhance our continuing efforts to improve the quality and proficiency of educational services at Moses Cone Hospital.

The medical teaching programs of the Moses Cone Hospital have clearly met their initial aims. The North Carolina AHEC program has enjoyed considerable success in health manpower development, with significant contributions from the teaching programs of Moses Cone. As this goal nears fulfillment AHEC's alternative purpose, health manpower maintenance or continuing education, will become its main justification. The effective delivery of continuing medical education to physicians in small communities will not directly influence the availability of health services, but it is rural North Carolina's best insurance for quality medical care. AHEC now faces a fresh and even greater challenge. It will require new and ingenious strategies if "state of the art" medical care is to be made accessible to all our citizens.

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Community Hospital Training Programs: Underrated Options for Medical Education

Jack D. McCue, M.D.

A majority of hospitals that sponsor graduate medical education are non-tertiary care community hospitals with fewer than 400 beds,[1] yet a review of medical education literature reveals no descriptive studies of community hospital training. The Association of American Medical Colleges and the American Medical Association, accumulators of valuable statistics on medical education, can provide only quite limited information since data on community hospital programs are not kept separately. Faculty advisors who assist students in their choice of a residency program generally have a limited understanding of community hospital-based training programs because most of their professional activities have been limited to university centers. For good economic, political, and educational reasons, community hospital programs will continue to be important sites for graduate medical education; a broader understanding of their characteristics, strengths, and problems, like those cited below, is needed.

Benefits of Community Hospital Training Programs

1. Education Flexibility. Unlike most community hospitals, university hospitals have powerful vested interests, traditions, and requirements for primary care manpower; as a result, university hospital residents' schedules seem to be more shaped by an institution's traditions and the requirements of subspecialty accreditation than deliberate and personal planning for the individual residents' needs. The format of the internship year, for example, is essentially unchanged at university centers despite major changes in the personal and educational content of internship. Community hospitals can be flexible enough to personalize graduate medical education without the schedule disruptions that university programs would encounter. In addition, small programs can more easily provide sane on-call schedules, accessible role models who have worked out a balance in their career, community responsibilities and personal life, and give the emotional support needed to facilitate maturation and the achievement of the difficult personal tasks of early adulthood[2, 3] than is possible at large programs where faculty is often transient and less committed to medical education than to research. Ultimately, more personal and humane treatment of residents will, I believe, result in more humane treatment of their patients.

2. Relevance to Medical Practice Needs. Community hospital programs are better suited to meet some of the essential educational needs of today's residents, especially in the important curriculum of primary care medicine. Even the future specialist who expects to spend his workday inserting small catheters into small coronary arteries soon discovers that most private practice specialists now must spend a substantial part of their time in primary care activities, a trend that will likely increase in the future. At most competitive university programs, the rarity of influential teachers who are experienced generalists (even within general internal medicine sections!) makes effective instruction in topics like common illnesses, practice management, or psychosocial issues commonly unavailable or deficient.[4]

3. Clinical Resources. Patients with undiagnosed and untreated problems are more likely to be encountered by community hospital residents. University hospital patients are typically evaluated thoroughly before admission, and most "fascinomas" never reach university centers now. Residents at community hospitals diagnose and treat tuberculous meningitis and brucellosis; severely burned patients with invasive pseudomonas cellulitis and refractory leukemias are more likely to be referred to university hospitals. Many common diseases are totally missed at a university hospital — a medical resident may, for example, never treat a typical case of infectious mononucleosis.

4. Continuing Medical Education. A major beneficial spinoff of community hospital training programs is increased communication between the university and practitioners through community-based educational programs. Because community-hospital-based faculty have a greater knowledge of the needs of practitioners, they can facilitate the design of continuing medical education that will actually influence patient care. Individual patient consultations for practitioners by the faculty are opportunities to teach by example the current opinions of what constitutes optimal medical care. Academicians also have much to learn from working with practitioners who are wise in the practical realities of private practice and properly skeptical of academic fads. Well-organized educational networks like North Carolina's AHEC[5] and Washington's WAMI[6] are examples of successful attempts to bridge the widening gaps in medical knowledge between the university and the practitioners through community hospital training programs.

Problems and Misconceptions

1. Fear of Competition. Community attitudes toward training programs are not uniformly supportive. Private practitioners and medical societies now often view community-based medical education as potential competition for patients and as a source of new physicians in communi-

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ties already experiencing a surplus — fears that are more pervasive than those outside private practice commonly realize.[7] In addition, patients in non-metropolitan areas are often less sophisticated about medical education than those who use university hospitals — they may still believe that students and residents are untrained, inexperienced, and unsupervised. Community hospitals, necessarily very sensitive to local public opinion, are wary of such misconceptions, and fear the occasional mishap by a student or resident that brings adverse publicity.

2. A Doubtful Solution to Excessive Specialization. It is unclear whether, as hoped, residents from community training programs are less likely to subspecialize. The reports that more medical residents decide to practice general internal medicine when off-campus experiences are included as part of their training[6, 8] could reflect just a national movement of graduate physicians into family medicine and general internal medicine, or perhaps the general influence of primary care training programs.[9] It is probable that, overall, personal factors play a larger role than specific educational experiences in the decision to specialize.[10, 11] Community hospital programs should, therefore, be supported for their own strengths, not because of their potential for correcting physician maldistribution or discouraging excessive subspecialization.

3. Ambiguous Faculty Academic Status. Faculty at community hospitals must struggle for recognition by the basic science oriented university faculty. Like divisions of general internal medicine and departments of family practice, community hospital faculty often fit uncomfortably into the current academic reward, retention, and promotion system. Publications, grant-catching ability, and national exposure, not the quiet scholarship, hospital service, and teaching efforts of community hospital faculty, are key to academic promotions and salary raises. While university department chairmen and deans seem now to be trying to recognize the special skills of off-campus medical educators, the system is still strongly slanted to retaining and rewarding faculty involved in basic science and high technology clinical research.

4. Not Cheap Medical Education. Unfortunately, community hospital training programs may well be more expensive than centrally-based university programs. Because there are fewer junior faculty members, fellows, and chief residents, and less subsidization of educational expenses by grants, foundations, and government funding, educational costs must be largely paid from patient-care revenues. One might even argue that resident training at university medical centers is a relatively inexpensive by-product of research and tertiary patient care. Excellent teaching requires a fusion of cultivated and practiced communication skills and a secure belief in one's teaching abilities that is not often found in unpaid clinical faculty. Outstanding clinicians, regardless of their expertise in patient care, are rarely an effective substitute for full-time teaching faculty who earn only part of their income in clinical activities.

Conclusions

The advisors and mentors of medical students need to know that community hospital residency training programs differ in many positive ways from their university counterparts, and can provide humane medical education that is responsive to individual residents' personal needs. Many expectations, however, that such education uniformly has broad community and university support, is less expensive, leads to fewer subspecialists, and can easily draw on inexpensive and expert skills of voluntary faculty are probably largely incorrect. Ultimately, the single most important role for academic community hospital programs will be to bridge the widening knowledge gaps between the university and the practitioner.

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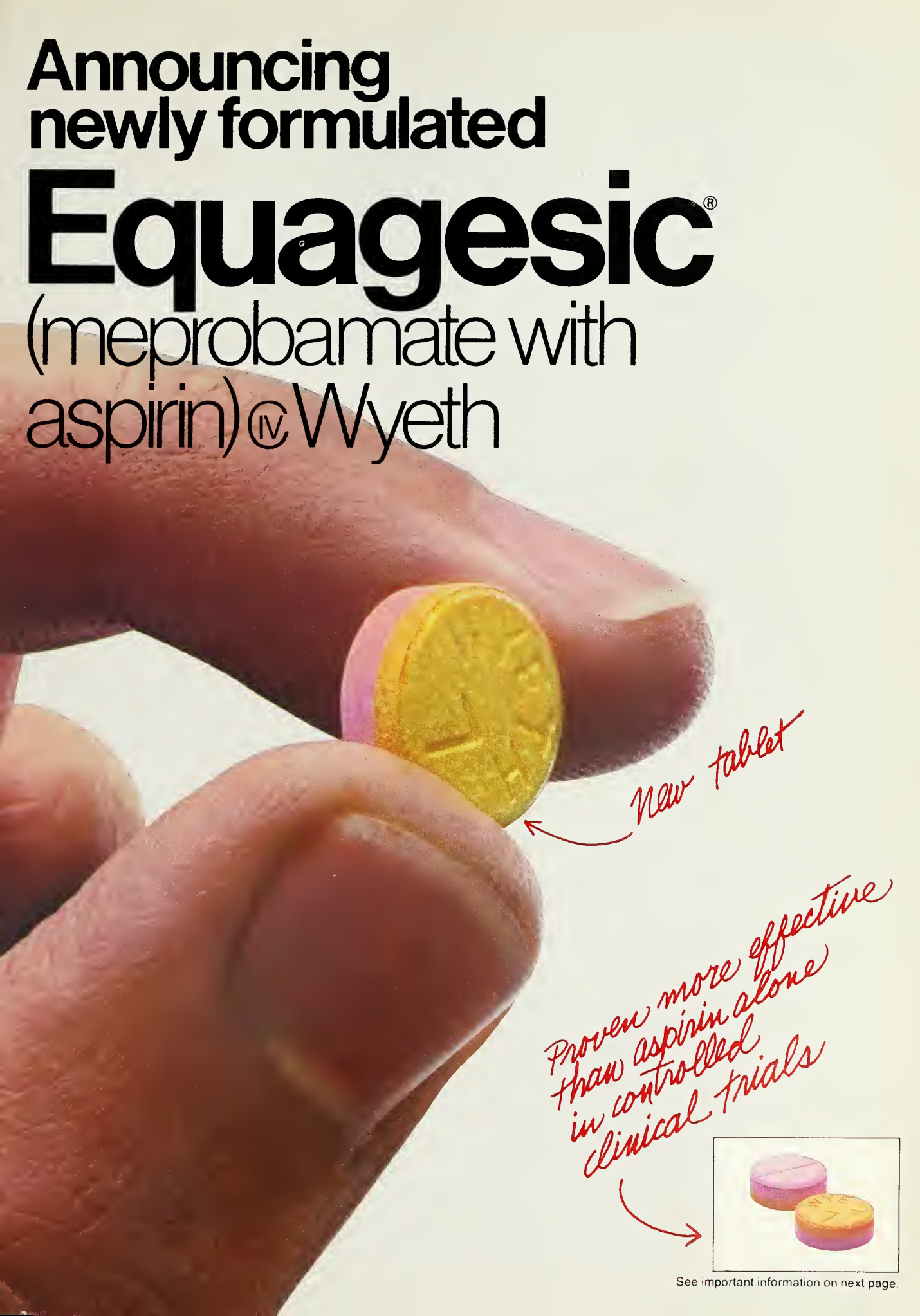
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accompanied by tension and/or anxiety in patients with musculoskeletal disorders.



when anxiety magnifies the perception of pain



1-2 tablet dosage 3 or 4 times daily

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(meprobamate with aspirin) ℞ Wyeth

(BRIEF SUMMARY)

DESCRIPTION:
Each tablet contains 200 mg meprobamate and 325 mg aspirin

INDICATIONS:
Adjunct in short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease. Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone. Effectiveness in long-term use, i.e. over 4 months, has not been assessed by systematic clinical studies. Physicians should periodically reassess usefulness of drug for individual patients.

CONTRAINDICATIONS:
ASPIRIN. Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE. Acute intermittent porphyria; allergic or idiosyncratic reactions to meprobamate or related compounds, e.g. carisoprodol, mebutamate, or carbromal.

WARNINGS:
ASPIRIN. Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE. DRUG DEPENDENCE: Physical and psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually, greater than recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms, e.g. anxiety, anorexia, or insomnia, or withdrawal reactions, e.g., vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinosis, and, rarely, convulsive seizures. Such seizures are more likely in persons with CNS damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation; symptoms usually cease within next 12- to 48-hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e.g., driving or operating machinery.

ADDITIVE EFFECTS. Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION:
An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug.

Meprobamate passes the placental barrier, it is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN. Keep preparations with aspirin out of reach of children. Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS:
ASPIRIN. Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE. Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney, to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS:
ASPIRIN. May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE. CNS: Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity.

GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate/mebutamate and meprobamate/carbromal. Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC"): Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms.

DOSAGE AND ADMINISTRATION:
Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSAGE:
Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdosage produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole-blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal. The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported. Acute simple overdose (meprobamate alone). Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS:
0.5-2.0 mg percent represents usual blood-level range of meprobamate after therapeutic doses. The level may occasionally be as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdosage, such as stupor or light coma.

10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment. Some fatalities occur.

At levels greater than 20 mg percent, more fatalities than survivals can be expected.

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol): Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated. Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption.

HOW SUPPLIED:
Scored tablets, bottles of 100; Redipak® strip pack 25's; Redipak® unit dose 100's, individually wrapped.

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One Community's Approach to Diabetes Education

Susan G. Drainville, R.N., B.S. and Robert E. Sevier, M.D.

RESPONSIBILITY for one's own care, a critical component in the treatment of chronic diseases, favorably influences prognosis and reduces acute hospitalizations. Indeed, self-management of chronic disease (with its prerequisite patient education) will likely be the rule, not the exception, as health care dollars and cost consciousness become the concern of both care provider and patient. In its search for quality education for those with one such chronic disease, diabetes mellitus, our community initiated a cooperative program to bridge the gap between hospital and community care. This collaborative program reduced duplication of services, pooled resources and provided patient services at less expense than could individual institutions or practitioners.

Community Diabetes Service (CDS) is an outpatient diabetes education and resource agency sponsored jointly by The Moses H. Cone Memorial Hospital, Wesley Long Community Hospital and the Guilford County Health Department in Greensboro, North Carolina. It serves the city of Greensboro and Guilford County, a metropolitan area in the Piedmont region of the state with an estimated population base of 320,000. CDS was founded in July 1981 with the following goals: 1) to provide direct teaching to patients and their families; 2) to provide in-service education and consultation to all members of the health care team; 3) to stimulate awareness of and community interest in diabetes; and 4) to meet the particular needs of the sponsoring institutions.

Background

There has been a long-standing recognition of the need for diabetes education in Greensboro. In the decade prior to the creation of CDS, some of these services had been provided on a part-time basis, initially by a unit of the United Way and later by a private home health agency. In February 1981, when such funding was no longer available, it became apparent that if a quality community diabetes education program were to continue, another sponsor needed to be found.

The Moses H. Cone Memorial Hospital was approached by several concerned physicians and citizens regarding support for a community diabetes education program. The hospital expressed interest in such a program but felt that it should be sponsored by more than one institution. Through the administrative support and personal efforts of the Moses H. Cone Memorial Hospital's Chief Executive Officer, a preliminary program proposal was drafted to include program objectives, functions, services, accountability and a tentative budget.

To draft the proposal, data on patients with diabetes in the Greensboro/Guilford County area were collected by a diabetes nurse educator from the city's four hospitals and the county health department for the period October 1980 through April 1981. The data revealed that, for the six-month study period, 1,269 patients with diabetes had been seen and treated in these facilities but only 174 had received follow-up education.

Establishment of CDS

At several meetings during May and June 1981, the program proposal and supporting data were presented to representatives of the four Greensboro hospitals and the health department. After due consideration, two of the four hospitals, The Moses H. Cone Memorial and Wesley Long Community Hospitals, and the Guilford County Health Department elected to participate in and to give financial support to a community diabetes education program. The proposed budget is depicted in table 1; approximately 12% of the necessary revenues were to be generated through the agency itself with approximately 38% each contributed by The Moses H. Cone Memorial Hospital and Wesley Long Community Hospital, and the remaining 12% by the Guilford County Health Department.

TABLE I
Budget for Community Diabetes Service

Salaries/Fringe Benefits		
Coordinator 25 hrs/wk	$11,775.00	
Clerk-typist 10 hrs/wk	2,000.00	
SUBTOTAL	13,775.00	
Conference/Travel	500.00	
Subscriptions/Supplies/ Education Materials	525.00	
Postage/Telephone	500.00	
Purchase of Literature for Sale	500.00	
Miscellaneous	200.00	
TOTAL EXPENSES		$16,000.00
Revenue from Sale of Literature	500.00	
Revenue from Private Consultations Charged at $10.00 per Visit and Anticipated Donations	1,500.00	
TOTAL REVENUE		2,000.00
BALANCE TO BE FUNDED BY SPONSORING ORGANIZATIONS		$14,000.00

From Community Diabetes Service, 1200 North Elm Street, Greensboro 27401.

Community Diabetes Service could thus begin operation in July 1981, following a organizational period of only three months. The Moses H. Cone Memorial Hospital provided leadership and enthusiastic support in spearheading much of the detail work required for program implementation and donated office space. Elaine Button, R.N., an experienced diabetes nurse educator, was hired as the initial Coordinator for CDS and remains in that capacity to the present. Recognized as an effective patient educator, Mrs. Button had held comparable positions with the United Way and a private agency that had provided similar services within the community.

The Coordinator of the CDS program operates under the supervision of an advisory board comprising representatives from each of the sponsoring institutions, a local physician, and a representative from the Greater Greensboro Chapter of the American Diabetes Association. She meets quarterly with the Board to present a report of agency activities, including statistics pertaining to clients seen and services provided. She also prepares an annual report which is circulated to the Board and to the Chief Executive Officers of the sponsoring institutions. Working with the Advisory Board, she has prepared policies and educational objectives for the CDS program and, drawing from her personal experience in diabetes education and that of similar programs throughout the country, has developed a curriculum for the community classes that are offered by CDS.

A community program like CDS is highly dependent upon support from local physicians who appreciate the value of quality patient education. When the CDS program began, the Coordinator visited physicians' offices to describe the agency and its role in the community and made presentations at medical staff meetings. In addition, flyers are distributed monthly to physicians and house staff, institutions, local industries, and the public libraries to remind them of the on-going diabetes classes.

CDS Services

Table 2 lists the services CDS offers. The community classes are presented free of charge as four two-hour sessions each month and are offered both during the day and in the evening, primarily at public libraries throughout Greensboro. The four sessions cover the many aspects of diabetes management for patients and their families who are either self-referred or referred by physicians or in-hospital patient educators. Individual consultations usually require a physician referral with specific prescription as to which aspects of diabetes management are to be covered (e.g., dietary instruction, insulin administration, blood glucose monitoring, foot care). Following an individual consultation, the referring physician receives a copy of the education plan utilized and the Coordinator's assessment of the apparent effectiveness of the effort. While no patient is refused services due to inability to pay, a modest fee is requested. In 1981 this fee was initially set at ten dollars for a consultative session which usually lasts about forty-five minutes; at present it is fifteen dollars for the initial consultation and twelve dollars for subsequent visits. These charges have allowed modest budget increases from time to time without the necessity for increased contributions by the sponsoring institutions. While Community Diabetes Service is primarily a patient education and consultative service, the Coordinator also plans diabetes educational workshops to update and refine diabetes management knowledge and skills for both health professionals and patients.

TABLE 2
Description of CDS Program

Outpatient:
1. Weekly classes (four-part series)
2. Individual consultations
3. Coordination of home care needs with patient, physician, other community resources
4. Home visits in unusual circumstances

Inpatient:
1. Discharge planning with hospital patient educators
2. Patient care conferences

Professional Education:
1. Education programs and resource materials to assist hospital staff to develop and refine nursing care of the patient with diabetes
2. Resource agency to nursing personnel and medical residents
3. Stimulation of research and study in diabetes among those interested in diabetes

Public Education:
1. Education programs planned to meet the needs of the community
2. Liaison with community agencies concerned with care of persons with diabetes
3. Lectures about diabetes for civic/lay groups

The Results

The success of the CDS program is reflected in table 3. During its first two years of operation, CDS has served 875 clients, either in classes or in individual sessions. The sponsoring institutions have continued their enthusiastic support of the agency, recognizing the value of their investment in quality education. For the physician who has limited contact with diabetic patients and inadequate office personnel and resources for effective teaching, CDS provides invaluable and inexpensive access to a highly skilled and motivated diabetes educator. It thus offers a way to avoid duplication of personnel and reduce overhead costs by providing a community resource to any practitioner with diabetic patients. As table 3 implies, there is a gratifying utilization and support of CDS by a broad base of community physicians. Patient acceptance and response also has been excellent, as reflected both in questionnaires and in improved performance demonstrated by appropriate pre-

TABLE 3
CDS Statistics 1981-1982

Total Clients Seen	1981-1982	1982-1983	Totals
Classes	301	307	
Consultations	93 (149 visits)	96 (163 visits)	
Discharge planning	27	44	
Home visits	7	0	
	428	447	875
Number of referring physicians	53	62	115

and post-testing. It is difficult to document reduced health care expenditures through avoidance of acute hospitalizations and reduced physician visits with CDS services, but we and participating physicians believe that initial hospitalization for education and instruction in self-management (e.g., insulin administration and regulation) has been avoided in a number of cases, and that the availability of intensive consultation through CDS has avoided re-hospitalizations.

In summary, the Community Diabetes Service program has efficiently and effectively met a growing community need in Greensboro/Guilford County since its inception in 1981. While such a collaborative effort is obviously not the only way to meet such a need, it is felt that CDS constitutes a model that may well prove useful to health care planners in other communities throughout the state as they seek to avoid duplication of services and to contain costs without compromising the quality of patient service.

Special thanks go to Elaine Button and James Brexler for their assistance in providing background information for this article.

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Understanding Hypertension

Martin Johnson, M.D. and Angela Staab, R.N.

Approximately 20 million Americans have undiagnosed or inodequotely treated hypertension (high blood pressure). It is known os the "silent killer" becouse the mojority of hypertensive people feel perfectly well. On both a national ond on indiviouol level, the first step toword correcting this heolth problem involves public educotion — we hope the following discussion will facilitate a better understanding of hypertensian.

How is the blood pressure measured?

Our blood pressure is created by (1) the farceful pumping of blaad inta the arteries by the heort ond (2) the tension in the wolls of the arteries (similorly, the water pressure in our hames is created by the force of the pump ond the size of the pipes the woter is pushed through). It con be meosured directly by surgically inserting o small pressure monitor into on artery, or indirectly (the usual woy) with o sphygmomonometer (blood pressure cuff) ond stethoscope. The sphygmomanometer cansists of on inflotoble rubber blodder inside an orm (or leg) cuff, on inflating bulb, ond a pressure gauge (monometer) from which the opplied pressure is reod. An accurote estimote of the blood pressure con be determined if the sphygmomonometer is properly calibroted ond the proper sized blood pressure cuff is used. A cuff thot is toa smoll far the arm will give o folsely high blood pressure reading ond a cuff that is too lorge will give o folsely law blood pressure reoding. The mast accurate kind of pressure gouge is usually the mercury-type pressure gouge, because it rorely needs recolibrotion; the diol-type pressure gouges con weor out eventuolly, ond they require periodic recolibrotion.

Ta measure the blood pressure, the proper sized cuff is secured snugly around the orm, which shauld be held at heart level. Enaugh air is pumped into the cuff to roise the blodder pressure high enough to actually (transiently) stop the blood flow through the orteries to the arm. Then, while listening with the stethoscope over on ortery ot the level of the elbow, the orm cuff is slowly deflated.

The indirectly meosured systolic pressure corresponds to the pressure reading (in millimeters af mercury) ot which turbulence, in the form of on initial tapping sound, is heard through the stethoscope. This is similar ta standing on o gorden hose and slowly releasing your weight; when woter begins flowing through the hose, turbulence (which could be "heard" with a stethoscope if your neighbors oren't wotching) occurs. The diastolic pressure corresponds to the pressure reading at which the tapping saund (and therefare, significant turbulence) disappears. The blood pressure is recorded with the systolic pressure on top ond the diastolic pressure below (far example 120/80 reods "120 over 80").

Emotional stress, excitement, exercise, tobacco, onxiety, and meols may all influence blood tronsiently, necessitating multiple blood pressure determinotions to establish on occurote estimote of the bload pressure. Thus, it is importont to be os comfortable os possible when the blood pressure is meosured, ond to ovoid eoting or smoking for o half hour before the meosurement. While everyone ogrees thot it is important to identify people with hypertension, it is just os importont not to mislobel o person os hypertensive with normol blood pressure because of inaccurote equipment or poor meosurement technique.

What are normal and abnormal blood pressures?

Over the post 15 yeors a number of importont scientific studies hove tried ta determine the "safe" blood pressure, rother thon "normol" blood pressure; this is because, in generol, the lower the blood pressure the better — there is no precise distinction between normol and obnormol blood pressure. Between 1967 ond 1970 the Veterons Administrotion reported the outcome of vigarously treoting diostolic blaod pressures between 105 millimeters of mercury (mm Hg) ond 129 mm Hg. Strake, congestive heart foilure, kidney foilure, ond eye domage were significantly reduced. Recent studies have demonstroted o reduction in heort ottacks even when diastolic blood pressures between 90 mm Hg and 104 mm Hg were vigorously treated. Bosed on this reseorch, it is recom-

From the Moses H. Cone Memorial Hospital, Greensboro 27401-1020.

mended that, if passible, everyane's diostolic bload pressure be maintained ideally below 90 mm Hg.

We now know that the level of the systalic blaad pressure is also on impartant risk factor for strake and heort disease, but the benefits of vigarously treoting systolic hypertension have nat been as conclusively demonstrated os they hove been for diostolic hypertension. A general recommendotian is to maintain the systolic pressure below 140 mm Hg in moles and 160 mm Hg in femoles (women are ot lower risk, it seems, for health problems from systalic hypertension). Other impartant factors that increase the risk of heart diseose include cigorette smoking, high bload cholesterol, and paarly controlled diabetes mellitus. All these risk factors ore mode much more dongerous by coexisting hypertension. Correcting each of these importont risk factors is on effective means af reducing one's future risk of vosculor disease. None af these carrections, however, has been proved to be as dramatically beneficial as normalizing persistently elevoted hypertension.

In summory, there is no normol blood pressure — 140/90 (which everyone calls "narmal") is really the highest blood pressure thot is, in generol, not ossociated with an increosed risk af strake, heort diseose, and kidney disease. As in golf, the lower the better!

What actually causes hypertension?

Mast people with persistently elevoted blaod pressure have no single or definable couse for their hypertension. It has been demonstrated that hypertensive people who are averweight can significantly lower their blood pressure by weight reduction, limiting dietary sodium, ond increosing dietary potassium. Anxiety ond nervousness, on the other hand, ore not on impartont element in causing persistent hypertension ond tronquilizers should not be used to treat hypertension. While mony nervaus people have high blood pressures, most do not, ond it has never been praved that onxiety couses blood pressure to be persistently elevated.

Rarely, a single cause for hypertensian is discovered (for exomple, kidney diseose or rore tumors) but this is the exception rather than the rule. Mast people with high bload pressure hove a genetic predisposition to hypertension (neorly oll hove a blaad relative with high blaod pressure, usually o porent or grandparent). The final "diagnosis" is idiopothic hypertension — idiapathic is a medicol code ward for "we don't know what reolly causes it, but we hove to call it samething."

How is hypertension treated?

The gool of therapy is to reduce the blaad pressure, if possible, below 140/90. Successful theropy begins with educatian, because the health core pravider and the patient must work os a teom to ochieve the therapeutic goal. Most people require exercise and dietary instruction to reduce their dietory solt intake and lase any excess body weight. A smoll percent of people with mild hypertension (diastolic bload pressures between 90-104 mm Hg) ochieve satisfoctory blood pressure control with these lifestyle chonges. To normalize blood pressure, hawever, most hypertensive people alsa require medicotian.

Antihypertensive medicotion basically folls into three categories: the diuretics (for example, hydrochlorathiozide) which force the kidneys to eliminote excess salt and woter; the vosodilotors (for exomple, hydralozine) which reduce tension in the wolls af blaod vessels; and the sympothalytics (for exomple, propronolol or reserpine) which reduce the forceful beoting af the heort. Ideolly, the fewest number of medicotions which accomplish the job is best but occasianolly two or three different medications ore required in cambinotian to reduce the blood pressure to on acceptoble level. Before the effectiveness of a medicotion con be praperly assessed, it must be taken os prescribed. Failure to take medicotian os prescribed is, by for, the most common cause for uncontrallable hypertension. Individuolized therapy, motivated and knowledgeoble patients, and o concerned heolth care pravider are the main ingredients of successful therapy.

Can medication be harmful?

Any medicotion con have side effects that con range from mild and tronsient nuisances to intolerable toxicity. Before toking medicotion o person should knaw what side effects to expect and what to do if they accur. Diuretics can couse o foll in the blood potossium level with resulting muscle weokness. This con be minimized by reducing the omount of solt (sodium) in the diet. The blood potossium should be meosured periodically while taking a diuretic. Vosodilotors con couse polpitotions (the sensotion of excessively ropid beating of the heort) ond weight goin from salt and water retention. To minimize the weight gain and increose bload pressure control, most vosodilotors ore combined with o diuretic. Sympatholytic drugs can cause drowsiness ond lightheadedness upon standing which usually resolves ofter continued use. Individuolizing theropy for hypertension means finding the most effective, leost expensive, eosiest to toke medicol regimen with the leost side effects. Most over-the-counter medicotions (including ospirin, Tylenol, ond cold remedies) can be sofely token with antihypertensive medicotion but if one is uncertoin, the phormocist should be consulted.

Does medication cure hypertension?

Medicotion unfortunotely cannot cure hypertension. Taken os prescribed, however, medicotion con keep the blood pressure at the desired level, but this requires lifelong therapy in neorly all cases. Abruptly stopping anti-hypertensive medication con result in o ropid rise in the blood pressure to dongerously high levels occasionally requiring hospitolizotion.

Self-Help for High Blood Pressure

C. Stewart Rogers, M.D.

Most persons who have sustained hypertension will require lifelong therapy with one or more drugs. There ore, however, millions of Americans with barderline or mild hypertension in whom the need for drugs is still controversial becouse of cost, uncomfortoble side effects, ond possible long-term harm. Even these mildly offected persons would benefit from lawering their blood pressure — but only if it could be done for a reasonable cost ond without mony side effects. There ore olso more people naw who wont to toke os much responsibility os possible for their own health, ond who are strongly motivated to use dietary or behavioral opprooches to minimize the use of drugs.

There are severol non-drug therapies that ore known to hove lowered the blood pressure successfully in mony persons, but it is very importont thot interested potients understond the issues. These opprooches ore not eosier thon toking drugs, they ore cleorly horder. They may or moy not be cheoper, ond they may not be free of side effects, especiolly short-term discomforts. Most importont, they moy be insufficient to fully normalize the blood pressure, ond thus may give folse reossuronce, especially if potients use initiol success with these oppraaches as an excuse for dropping out of medical follow-up core.

On the plus side, anti-hypertensive methods like diet, exercise, ond stress control moy confer heolth benefits beyand blaod pressure reduction. Some of the benefits for physical heolth ore speculotive, but there is strong indirect evidence thot the cardiovoscular system improves in efficiency and in resistance to the cammon degenerative diseases by these self-help programs. Most scientists and other observers would ogree that successful diet and exercise programs also confer psychologicol improvements in self-esteem ond sense of well-being. By controst, pills moy cause modest reductions in metobalic ond cordioc vigar, moy impoir sleep ond mood, ond may couse some persons to feel a loss of personol control or responsibility for their body.

The non-drug methods ovailoble for blood pressure lowering are behaviorol ond dietary. The first cotegory hos many techniques, ronging from simple reloxotion to mojor life changes for stress reduction. In between ore complex progroms of meditation, serious exercise progroms, ond psychotheropy. Potients hove o variety of motivotions for undertoking behoviorol treotment besides blood pressure reduction, and there moy be mony odditionol positive outcomes. But it is olso cleor thot these opprooches require tremendous commitments of effort, time, ond other resources. Since there are so mony behoviorol opprooches, and since most involve highly individual voriations, the effects on blood pressure have been hord to study. The ottempts thot hove been mode hove produced mixed ond confusing results; each technique studied has achieved some successful outcomes in smoll numbers of highly-motivoted potients. In mast coses, however, it is impossible to ossess the contribution of concurrent diet or other chonges, ond it is not known if the reported blood pressure control is a long-term improvement.

Diet theropy has been somewhot eosier to study ond there is more confidence in the scientific medicol community thot weight control ond solt restriction are effective treotments for hypertensian. Obesity is commonly found in hypertensive potients, ond substontial weight loss lowers blood pressure, often to normal. A successful weight control experience for on obese person is likely to be ossociated with other positive chonges (exercise, self-esteem), ond reducing the amount of food eoten usuolly reduces sodium intoke os well.

Solt restriction is the most effective of oll non-drug theropies, ond wos used successfully before ony ontihypertensive drugs were developed. Severol coutions ore in order: 1) only a smoll drop in blaod pressure can be expected unless sodium restriction is severe, 2) not every potient will respond, ond 3) the benefit losts only as long os the diet is continued. On the other hond, Americons consume, on the overage, over ten times the amount of sodium their bodies require far good heolth, ond several times the amaunt consumed by some cultural groups in whom hypertensian is unknawn. A few simple changes in shopping and cooking hobits con dromoticolly reduce salt intoke; these need not involve stronge or more expensive foods. The chort compares the sadium content of similor foods.

Comporison of the Sodium Content in on Averoge Serving of Common Foods

Food	Sodium Content (mg)	Food	Sodium Content (mg)
Fresh pork (4 oz)	93	Hom (4 oz)	1,400
Fresh or frozen green vegetobles	1-3	Conned vegetobles	220-320
Oronge juice (6 oz)	4	Tomoto juice (6 oz)	650
Ootmeol	1	Boxed cereols	250-350
Apples, oronges, peors	2-3	Pickle (1)	1,000-2,000
Ground beef (4 oz)	76	Conned soup (1 cup)	850-1,100
Swiss cheese (1 oz)	74	Americon cheese (1 oz)	406

From the Moses H. Cone Memoriol Hospitol, Greensboro 27401-1020.

A serious attempt to lower sodium in the diet requires some effort and study. Pamphlets and low salt cookbooks are available from the American Heart Association or your local hospital dietition. A low salt diet progrom is best approached as a deliberote plon for the whole fomily ond should probably include some attention to reducing saturated fats and cholesterol, as well as increasing fiber. Most people will miss salt for a time, ond will be much happier if their diet plan includes experimentotion with alternotive spices. Soltsubstitutes help some people tolerate low salt diets, ond developing a taste for fresh fruit as snocks will go a long way toword meeting all heolthy dietary goals.

Dietary changes, while not easy to occomplish, may be enough to avoid hoving to take drugs for mild or borderline hypertension, should reduce the number or dosage of medications required in more serious hypertension, ond will reduce the potassium loss in those who toke diuretics for high blood pressure. Chonges in dietary fot ond fiber content will give benefits beyond blood pressure control, and other family members, especially children, may leorn good habits that will ultimately prevent hypertension and other cardiovoscular problems in themselves.

Varicose Veins

C. Stewart Rogers, M.D.

Long-standing problems with lower leg veins ore very common among young and old alike, and moy seem more serious to the potient than to the doctor. Most of the problems roised are cosmetic due to visible or bulging veins, bruising, or brownish splotches, but uncomfortoble symptoms or serious skin breakdown often occur as well. Some of these problems respond well to surgery, but some do not, ond it con be difficult to leorn the best non-surgical woys to relieve symptoms.

First of oll, we are tolking about two different diseases that are only superficially alike. *Varicose Veins* ore a simple disease of unknown cause, in which the veins just under the skin are bulging ond very disfiguring. The disease is "simple" in the sense thot the deep veins are usually normal, the blood drainoge from the leg is adequate, ond therefore the skin itself is not harmed. There con be some aching pain, especially after prolonged standing, but the chief problem is cosmetic.

The choice of therapy is olso simple. For some patients long trousers or stockings may solve the cosmetic problems, and brief periods of rest from standing may eliminate the pain. Support hose, even the routine store brands, may give added comfort. The only definitive treotment, however, is surgical removol of these superficial veins or injection of a solution thot will scar them closed. This lotter choice is not usuolly as successful in the long run, and is not ovailoble in many parts of the U.S.

The other diseose is *Chronic Venous Insufficiency* which usually results from the domoge left ofter on episode of blood-clotting in the leg veins (phlebitis). It moy follow injuries or fractures, or occasionally it develops without a known couse. Bosically the damage is to the mechonism that supports a smooth flow of blood uphill back to the heort, ond results in much higher pressure in the veins. This, in turn, causes fluid to build up in the lower leg which leods to chronic skin disease with itchy rashes, discoloration, ond ulcers. There may be a serious problem with poin on standing, described by patients as a "bursting" sensation.

Surgery will not improve this situation. Although at times the superficiol veins are swollen to some degree, this is caused by malfunctioning deep veins that are beyond repair. This is a lifelong problem thot connot be cured, but it con be greotly relieved in fairly simple woys. The problem is to reduce the pressure from within the veins, and to reduce the fluid occumulotion in the onkles and legs.

Treotment requires o combinotion of leg elevation ond high-pressure stockings. Elevotion of the legs moy be effective in mild cases if the patient con orronge the time necessory. The feet must be above the heort as long ond os often os needed to control poin and swelling. Stockings ore needed in most coses, and must be medical-strength (prescription) hose to overcome the abnormolly high pressure in the veins. These moy or moy not require speciol fitting depending on the shape of the legs: whot motters is firm pressure without a constricting band at the upper calf or thigh (which could make swelling worse and even couse phlebitis!).

Diuretics or fluid-pills usuolly do not help much unless there is another disease, like kidney or heart diseose, contributing to the fluid. Persistent rashes or leg ulcers require speciol medicol attention, but the moinstoy of therapy is still reduction of pressure and fluids to allow normol heoling. As in so mony other chronic diseoses, the patient has the mojor role to play in controlling symptoms ond preventing complicotions.

From the Moses H. Cone Memoriol Hospitol, Greensboro 27401-1020.

EDITORIAL

Grass Roots Medical Journalism

Jack D. McCue, M.D.

STATE medical journals are caught in a pinch. Increasing competition from the popular "throwaway" journals makes it difficult for these modest publications to support themselves through advertising income, and the number of journals physicians receive through subscriptions and mass mailings makes most of us unwilling to pay for or even read yet another. Our state medical journal does serve special purposes, however, and we should be reluctant to let it go unread or simply atrophy — it keeps us in touch with our colleagues in other locations, and can inform us of medical, political, and social issues that are important to North Carolina physicians. Can we help make the *North Carolina Medical Journal* more worth the effort and expense?

Snappy covers, catchy titles, and readable articles that have special relevance to North Carolina physicians are an obvious response to making a state journal more popular — changes that have already been made with great energy and good results by Dr. Stead. The novel idea of including parts of a journal that can be left in the waiting room for patients to read is especially meritorious. Ultimately, however, a state journal will flourish or wither on the basis of its scientific, editorial, and historical content — articles with relevant, interesting information are required to keep it alive. A personal experience as guest editor of the *Maine Medical Journal* taught me some things that I thought might benefit the *North Carolina Medical Journal* — hence, this month's issue from Moses Cone Hospital.

All hospitals have repressed or budding scholars and researchers — innovation is not restricted to the ivory towers of academic medicine. Publishing insights from one's practice experiences or the results of community hospital research, however interesting they may be, is another matter. It takes good writing skills, access to statistical analysis, a great deal of secretarial time, personal determination, good luck, and often an academic reputation to get case reports and studies published in refereed journals. To encourage practitioners in Maine to publish their shoestring research and case reports, the *Maine Medical Journal* decided to diffuse the responsibility for the monthly issues to the ten medical centers. Each major hospital was responsible for one issue of the journal yearly, and there was always a good soul who would take on the job of being guest editor to coordinate the efforts. The result was that each issue contained a yearly synopsis of the research and innovation from a different community hospital — valuable, often otherwise never-to-be published information.

Could the *North Carolina Medical Journal* use the multiple medical center (i.e., AHEC!) approach to medical journalism? Will someone in Wilmington, reading of Ms. Drainville's and Dr. Sevier's approach to diabetes education be inspired to start such a program? Will other neonatal ICUs look at the issues involved in preventing deafness, as Dr. Boer did? Will experienced practitioners reexamine their years of experience and record their clinical and philosophical insights that they have always intended to write down, as Dr. Freedman did?

Decentralizing the *North Carolina Medical Journal* to some degree might actually stimulate research, scholarly activity, and a greater awareness of the need to examine critically our own local experiences with medical care. It may stimulate readership because it would truly highlight what is happening in medicine in North Carolina — not just what is happening on the medical school campuses.

From Moses H. Cone Memorial Hospital, Greensboro 27401-1020.

Time Will Tell

Eugene A. Stead, Jr., M.D.

SHOULD Dr. McCue and I have accepted the paper by Arthur Freedman? He goes against conventional wisdom in stating that symptoms usually interpreted as resulting from the interaction of a normal brain with any adverse environment are in fact the output of an abnormal brain and that this output is relatively little influenced by environment. The only evidence presented is anecdotal and is based on his many encounters with complaining patients. I voted for acceptance because (1) it gives us a vignette of one person's view of North Carolina medicine; (2) all wisdom doesn't reside in medical centers; and (3) perceptive persons may lead the way for future scientists.

The tie between structure and function is of course obligatory. When two brains have different outputs, one can safely assume they have different structures. The cause of the difference is the question at issue. Conventional wisdom states that the structure of the complaining brain can be returned to normal by a variety of psychotherapeutic and environmental maneuvers. Freedman's experiences led him to believe that the abnormality is not reversible by these maneuvers and that the structure of the brain must be changed if its output is to be affected. He elects to change the structure by attaching chemical moieties to it.

We know from our experiences with diseases and drugs that the structure of the brain can be altered by adding or removing materials that are too small to be detected by electron microscopy. The psychosis of Cushing's disease or myxedema is undoubtedly due to changes of this nature. Drugs causing changes in the outputs of the nervous system produce their effects by attaching to receptors in the nervous system in a way that alters their structure. Again, these changes in structure are submicroscopic.

My own bias is that Freedman will be proved correct in his thesis that the brains in his subsets of complaining patients are different from those of the non-complaining population. Contrary to him, I believe that the abnormalities in these brains are made obvious by environmental, cultural, and socioeconomic influences, and by the behavior of doctors who treat them in the framework of a variety of illnesses. There are many irreversible structural defects that become obvious only on appropriate testing. Color blindness, slow social learning, dyslexia, G6PD deficiency, and many allergies remain unknown by microscopic examination but become obvious by appropriate testing.

I am skeptical about Freedman's conclusions about therapy. I have regarded these persons as non-progressive variants from the average and have cared for them in the framework of health rather than illness. Time will tell which of us is correct.

Why Dependency Is Increasing

Eugene A. Stead, Jr., M.D.

THERE was a time when many believed that some combination of education, science and technology would reduce disability and make our welfare society a thing of the past. This is a dream that has not come true. What went wrong?

The stresses induced by independent living have exceeded the gains in performance produced by education. To function effectively in our increasingly complex society, each person has had to increase the number of persons with whom he interacts each day. Energy is lost in person-person interfaces and there are more opportunities for the development and expression of hostile feelings. Wear and tear on our bodies generated by hostile brains has a cumulative unfavorable effect on our bodies. This leads to illness and dependency.

The rate of change in our daily lives has increased with the progress of science and technology. Persons who could function independently in a simpler society have become dependent as their skills became obsolete early in their work life.

Our industrialized society has generated environmental hazards that increase dependency. Cigarette smoking, alcoholism, automobiles, machines that maim, asbestos exposure, drugs, air pollution, etc. have enlarged the rolls of the disabled and dependent.

Changes in social custom that permit males to renounce the lifelong support of their female partners and their children lead to dependency. This may in the end be the final straw that leads to complete socialism.

In his Special Article elsewhere in this issue of the *Journal,* Dr. Busse emphasizes yet another important factor creating more dependents — namely, aging. The optimistic had hoped that when persons lived longer they could work longer. The data presented by Busse indicate that a decline in mortality does not necessarily signify a decline in work disability. In 1970, 15% of individual men between the ages of 60 and 65 were unable to work. In 1980 the figure had increased to 18.9%. In 1970, in the age group of 65-69 years, 21.9% were unable to work. In 1980 this figure was 25.2%.

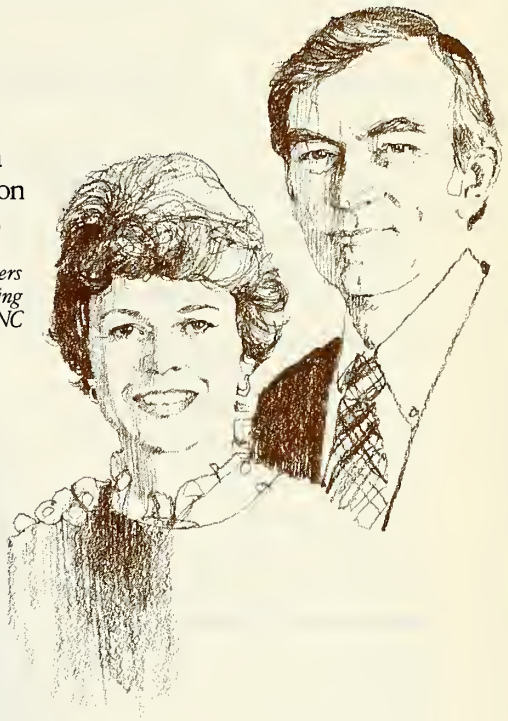
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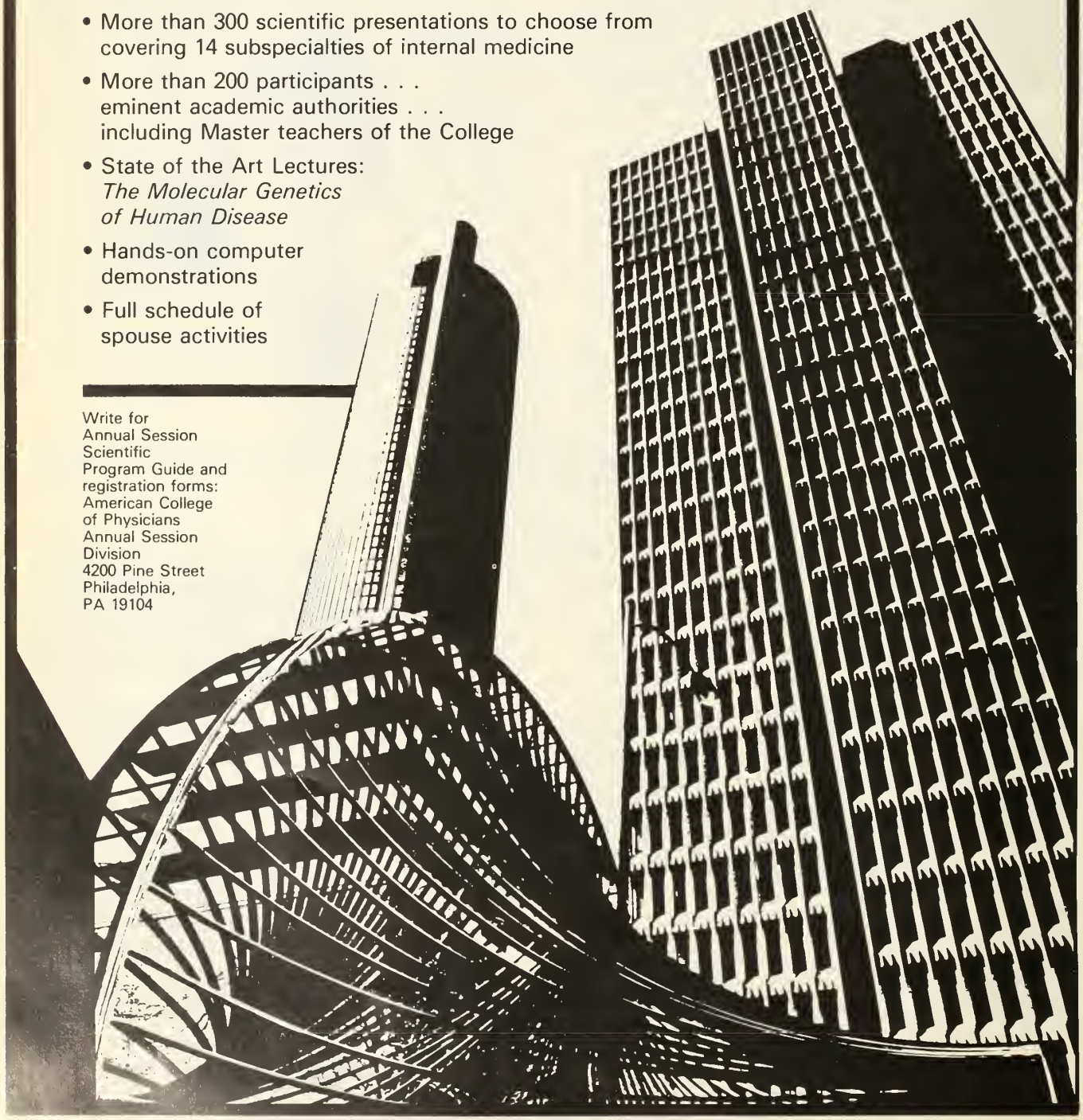
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SPECIAL ARTICLE

Longevity, Disability, and Retirement

Ewald W. Busse, M.D.

THERE is a rapidly increasing number of people who are living longer than at any time in the past 2000 years. It is usually assumed that longevity is accompanied by a proportionate increase in the productive work years, followed by a period of retirement that is relatively free of disease and disability. This optimistic assumption has affected planning by both public and private committees and commissions. Unfortunately, evidence has existed for some time that the extension of life span in the United States and throughout the world has not been accompanied by a significant delay in the onset and the severity of chronic disease and disability. The assumption that improved health and a longer life span are synonymous has played a role in altering eligibility for Social Security benefits, other health and retirement plans and benefits, and the law by raising to 70 years the age for mandatory* retirement.

The National Commission on Social Security in its March 1981 report stated, "The Commission anticipates that increased longevity will be accompanied by a corresponding increase in active life." However, a minority of the Commission contended that "the evidence does not support any claims that longer life is equivalent to longer years in good health." A similar cautious view was expressed in the 1983 Report of the National Advisory Council on Aging of the National Institute of Aging.[1] According to the 1982 National Plan for Research on Aging, "There is no substantial evidence that the elderly of today have better or worse health than the elderly of yesterday."[2] Thus, the influence of Medicare is negligible. Although an optimistic viewpoint does have value, and it is quite possible that in the years ahead there will be improvement in the functional capacity of older people, this optimism, if not put in balance by reality, could result in poor planning for maintaining and improving the health and well-being of the elderly.

Life Expectancy

Life expectancy at birth is a prediction based upon assumptions, such as no major changes in the organization of medical care or preventive public health measures, no catastrophic change such as war or an epidemic, and no substantial change in environmental, social, or economic conditions. Life expectancy at birth in the USA in 1982 was 70.8 years for males and 78.2 years for females. A white male 65 years of age can expect to live 14.4 years, a female 18.8 years. The prediction for life expectancy in the year 2000 is 73.42 years for men and 81.05 years for women. These changes in life expectancy are important for our planning but are likely to result in an overwhelming problem for the developing nations of the world.

The World Population

As of 1980, the U.S. population was 227,658,000 (Myers, 1983 [reading from material of the 1980 Bureau of the Census, personal communication]) and the total world population was estimated at 4.4 billion (4,432,100,000). Of this world population, 375,800,000 are 60 years of age and over; 45.4% are living in more developed nations, and 54.6% in less developed nations. By the year 2000 there will be a remarkable change. Only 39% of older persons will be living in developed regions and 61% in less developed regions. There will be an increase of over 200,000,000 old people in slightly fewer than 20 years. Of this increased number, 155,000,000 will be living in the less developed regions.

Male-Female Differences

Inasmuch as women outlive men, Feldman presents some very interesting data regarding the ability to perform specified activities.[3] These include such things as the use of fingers, stooping, crouching or kneeling, carrying or lifting 25 pounds or more, or standing for long periods. The percentage of women between the ages of 35 and 65 that have difficulties with these activities exceeds that of men. Women use physicians and medical facilities more frequently than do men. Women have more minor disabilities than men, but have fewer major disorders that are life-threatening.

Changes in living habits could affect morbidity and mortality. The reduction in smoking and the improvement in personal health habits may alter the prevalence of disability and may change the mortality rates. Feldman refers to "the compression of infirmity." This is the hope of gerontologists who not only want to prolong life, but want to reduce infirmities so that the decline period preceding death will be shortened.

There are sex differences in the morbidity and mortality ratios in the three major cardiovascular diseases. These are coronary heart disease, hypertension, and vascular lesions of the central nervous system (stroke). In the U.S. coronary heart disease is the cause of death in twice as many men as women. Stroke is somewhat higher in men than in women, but hypertension is essentially the same for both sexes. These differences suggest that although there may be some causative factors in common between these three disorders, they are far from identical.

In the U.S. the high mortality of males compared to females appears to be a complex interaction between ge-

* Amended January 1, 1979, the Age Discrimination in Employment Act of 1967.

From the Department of Psychiatry, Duke University Medical Center, Durham 27710.

netically determined physiological differences, socioeconomic factors and cultural values. Behavioral expectations and environmental conditions may also be more dangerous for the man than for the woman.

Chronic Disease and Disability

Eighty-six percent of older people have some form of chronic disease. The most frequently recorded chronic conditions are arthritis, heart problems, hypertension, diabetes, brain impairment, and vision and hearing defects. However, only 5% of those not in institutions are housebound, and only 1% bed-ridden. The over 65 age group averages 16 days per year confined to bed. Most confinements in the older group are attributed to chronic conditions rather than to acute illnesses. Mental disturbances are common affecting approximately 10% of the population over 65 and 20% of those over 80. Of those in nursing homes, one-half suffer from some degree of intellectual impairment. In addition to organic brain disease, the most frequently reported mental conditions are chronic depression and anxiety.

To care for these increasing and disabling health problems, older people make more frequent use of medical services both as inpatients and as outpatients. They account for 15% of all doctors' visits, 25% of all prescriptions, and 34% of all days in short-stay hospitals. It is evident that older persons do suffer from acute disorders as well as exacerbations of chronic disorders, and these do require hospital attention. They are hospitalized for much longer periods of time than are young people, and surgical procedures have increased more among people over 65 than in any other age group.

Longevity and Disability

A National Survey of the Aged[4] was conducted in 1962 and repeated in 1975. Medicare became effective in 1966; therefore, this report provided an opportunity to determine (1) whether Medicare affected how old people function, (2) how old people feel about their health, and (3) whether Medicare and other social programs of health services have made a difference in the provision of direct services to the elderly sick.

In this study an index of incapacity was developed. The old person was asked specifically: Can you go outdoors? Can you walk up and down stairs? Can you get about the house? Can you wash and bathe yourself? Can you dress and put on shoes? Can you cut your own toenails? The answers to these questions were scored on the basis of (1) without difficulty, (2) with minor difficulty, or (3) with the help of another person. In both 1962 and 1975 the proportion of those with no incapacities remained the same — 7 of every 10 were able to perform all of the tasks. However, there was a difference in that incapacitated elderly people were more likely to have seen a doctor in 1975 than in 1962. Six of every 10 had seen a doctor during the preceding month in 1975, five of every 10 in 1962.

Nursing Homes

Between 1974 and 1978, the number of nursing home residents increased by more than 21%. Some 20% of the aging will enter a nursing home before dying. It is projected that nursing home residents will increase 54% by the year 2000. For persons 65 years of age and over, the median age in nursing homes was 81 in 1977. Forty percent of the elderly nursing home residents were 85 years of age and over. The ratio of women to men was approximately 3 to 1, and approximately 93.2% were white. Nursing home use is nine times higher among unmarried than among married elderly persons.[2]

Causes of Death

Since 1950 there has been a substantial shift in the ranking of the leading causes of death among those 65 years of age and over. In 1983, the major causes of death in this age group are listed as heart disease, malignant neoplasm, cerebrovascular disease (stroke), followed by influenza and pneumonia. Other frequently reported causes of death are arteriosclerosis, diabetes mellitus, and accidents. Although heart disease has declined, it remains the predominant cause of death and continues to increase with advancing age. Heart disease produces 51.5% of the deaths between 65 and 75 years, 61.1% between 75 and 84 years and 70% after the age of 85. In contrast, the percent of malignant neoplasms as a cause of death declines with advancing age. Malignant neoplasms produce death in 26.4% of those aged 65 to 74, 18% between the ages of 75 and 84, and 9.9% after the age of 85.[5, 6]

The diseases listed as the most frequent causes of death in late life are often not the diseases that result in long term care. Other conditions such as arthritis and organic brain disease are the basis for serious disabilities.

Health and Retirement

The designation of a "normal" retirement age has been said to be the age at which people are no longer "sufficiently healthy to function in their jobs."[3] Health status is a major consideration in flexible retirement, but mandatory retirement, usually at age 65, was not primarily linked to any functional capacity but rather to the size of the labor force and the economic situation.[7]

The prevalence of ill health and its effect on work incapacity is of major importance. The proportion of men in the 50-60 age segment who were unable to work because of illness increased between 1970 and 1980. In a more detailed breakdown, it appears that among individuals between the ages of 60 and 65, 15% were unable to work in 1970 and this increased to 18.9% in 1980. In the age group 65-69 years, 21.9% were unable to work in 1970 as opposed to 25.2% in 1980. Feldman presents other evidence that indicates that "a decline in mortality does not necessarily signify a decline in work disability."[3]

The question is, how did this paradoxical situation occur? The death rate from myocardial infarction has been declining in both men and women. However, because individuals with myocardial infarction are likely to have a number of other chronic disabilities, it is probable that eradicating death from myocardial infarction would increase the size of the pool of disabled survivors. The control of other diseases such as diabetes may also contribute to the increasing number of individuals with infirmities that limit activity.

The length of work years is affected by a number of

factors including health, socioeconomic class, and type and place of work. Those with less education are likely to be in more physically demanding jobs. Assuming that people become better educated, this would mean that there could be a decline in work disabilities. However, one also has to recognize that with changes in technology a substantial number of jobs will be more mentally and emotionally demanding. In the future psychological stress may play a significant role.

The 1979 law affecting mandatory retirement and raising the age for receiving maximum Social Security benefits is in part an attempt to reduce the deficit facing the Social Security system. A shift of just one year in the average length of retirement raises or lowers the Social Security deficit by nearly $350 billion. There has been a steady increase in the number of retirement claims filed with the Social Security Administration by people who wish to retire between the ages of 62 and 64. Between 1947 and 1979, there was an important decrease in males 65 years of age and over who were continuing to work. Forty-eight percent of males over 65 were working in 1974. This had dropped to 20% in 1979. Working females 65 and over have remained at a constant 8%. The so-called dependency ratio, that is the ratio of people 65 and over to people aged 18-64, will continue to change. In the 1950s this ratio was 7.5 workers for every person retired. At present, there are approximately five active workers for every retired worker, but by the year 2030, this will be reduced to three workers for every retiree.[2]

Summary

Assuming that the number of elderly and their life expectancy continue to increase as predicted, and if disabilities are not considerably reduced from the current population, there will be a sizable segment of our population in the United States and throughout the world suffering from chronic disease and disability. To avoid further demands on already overburdened resources and a reduction in the quality of life, immediate and substantial investigations must be undertaken.[8] Research is needed to identify the causes of chronic disease and to develop preventive measures, treatment, and rehabilitation.

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Q: Elevated Serum Creatine Kinase (Does/Does Not) Equal Myocardial Infarction?

Linda M. Frazier, M.D. and Francis A. Neelon, M.D.

A: Not all that glitters is gold. Likewise, not all patients with elevated serum creatine kinase (CK or "CPK") are having a myocardial infarction. The following case shows how physicians can be fooled:

A sixty-one-year-old woman with a long history of manic-depressive disorder was admitted to a local hospital because of marked paranoia and hostile behavior. A routine chemistry profile revealed a CK of 718 mIU/ml (normal: 25-235) with a muscle-brain (MB) fraction of 6.4 percent (normally not present), but she denied chest pain and had no history of heart disease. There were no cardiopulmonary abnormalities on physical exam. She was transferred to the coronary care unit and treated for an acute myocardial infarction. CK rose over the next two weeks to 1040 mIU/ml but CK-MB fell to 0 percent. Lactate dehydrogenase isoenzyme II was never elevated, varying from 27 to 33 percent (normal: 29-37). Electrocardiograms were normal except for nonspecific ST-T changes.

Subsequently, serum thyroxine was found to be 2.3 μg/dl (normal: 4-12) with a triiodothyronine resin uptake of 30 percent (normal: 34-44). Although these values are consistent with thyroid gland failure, the thyroid stimulating hormone (TSH) of 2.7 μIU/ml was not appropriately elevated (normal: less than 6.5). No endocrine diagnosis was made and she was transferred to Duke University Medical Center for treatment of her psychiatric condition and further evaluation of her thyroid disorder.

She denied cold intolerance; there was no change in hair or skin texture or in bowel habits. She was somnolent but oriented. Visual fields were normal; skin was dry; there was no edema. She was diffusely weak; tendon reflexes were absent. CK was 443 U/l (normal: 20-120).

On the basis of the clinical exam, she appeared to be hypothyroid in agreement with her depressed thyroxine and triiodothyronine resin uptake. But her TSH was not elevated. Primary hypothyroid patients with a normal hypothalamic-pituitary axis produce marked elevations in TSH in an attempt to stimulate the secretion of more thyroid hormone. We suspected that the patient had pituitary failure, and carried out a battery of pituitary function tests.

To test the ability of the pituitary to secrete TSH, we gave intravenous thyrotropin releasing hormone (400 μg). The results showed that the pituitary was not functioning properly because TSH did not rise above 5.1 μIU/ml from a baseline of 4.8 μIU/ml (normal response: greater than 6).[1] Nor was the pituitary able to produce adequate levels of gonadotropins: follicle stimulating hormone was 7.0 mIU/ml and luteinizing hormone was 6.3 mIU/ml (normals for postmenopausal women: greater than 40 mIU for both hormones).

In order to test pituitary production of adrenocorticotropic hormone (ACTH), adrenal cortical function was first assessed by a cosyntropin stimulation test. We gave intravenous cosyntropin (250 μg); the patient's adrenals produced a prompt and normal rise in serum cortisol to a peak of 65.3 μg/dl. Then, the ability of the pituitary to stimulate adrenal cortisol production (i.e., to secrete ACTH) in response to stress was measured. We gave regular insulin (0.1 U/kg body weight) intravenously to create hypoglycemic stress. Serum glucose fell to 35 mg/dl (normal: 75-110), but serum cortisol only rose to 7.7 μg/dl from a baseline of 6.3, indicating pituitary ACTH dysfunction (normal response: cortisol rise over 15).

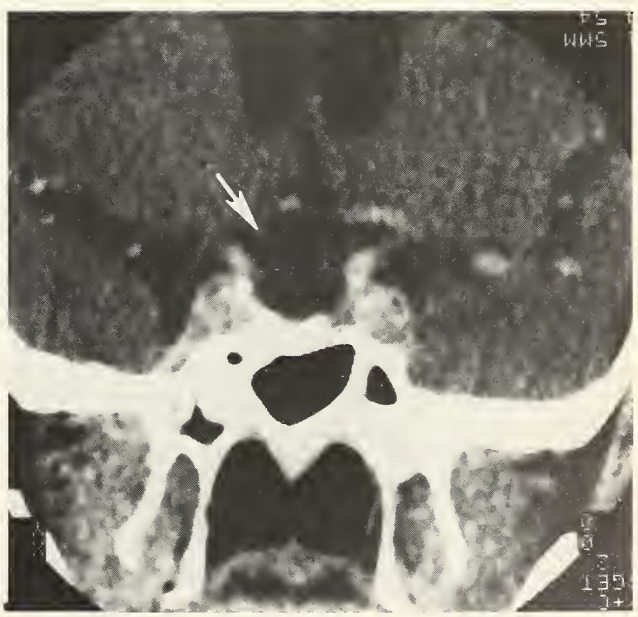


Figure 1. *Computerized tomography of the patient's sella turcica. This is a coronal section of a contrast study. The ventricles are visible at the top, and the arrow points to the pituitary fossa. The material in the fossa is of the same density as that in the ventricles, consistent with "empty sella."*

From the Department of Medicine, Duke University Medical Center, Durham 27710.

These studies document panhypopituitarism preventing the patient from producing adequate levels of TSH, gonadotropins or ACTH. Computerized tomography of the sella turcica (figure 1) was consistent with "empty sella." Since empty sella is a benign anatomical variant, this finding cannot explain the pituitary dysfunction and further evaluation is planned. Meanwhile, she was begun on cortisone acetate and thyroxine replacement and serum CK fell.

This patient has an unusual type of hypothyroidism due to generalized dysfunction of the pituitary gland. Her hypothyroidism undoubtedly caused the elevated CK since elevated CK levels are found in the serum of 66 percent of hypothyroid patients. The degree of elevation is related to the duration and severity of hypothyroidism. The elevated CK is felt to originate in muscle, because it is primarily of the muscle-muscle (MM) fraction, and because hypothyroidism is often accompanied by a neuromyopathy. Nevertheless, two-thirds of hypothyroid patients do have mildly elevated CK-MB fractions, ranging from 0.8 to 13 percent of total CK. This may be due to a mild cardiomyopathy, known as "myxedema heart." Sixty percent of hypothyroid patients also have elevated serum aldolase activity.[2]

There are other important causes of elevated serum CK which can lead to an incorrect diagnosis (table 1). Skeletal muscle trauma, seizures, rhabdomyolysis, myositis, and muscular dystrophy can elevate serum CK activity.[3] Alcohol intake can raise serum CK; elevation is mild in chronic alcoholism, modest with acute intoxication, and may be very high in delirium tremens. Muscle biopsy may show degeneration and necrosis when acute alcohol intoxication is accompanied by muscle pain and swelling.[4] Concomitant alcohol use may account for the elevated CK seen in some acutely psychotic patients, although others suspect the enzyme may be released from the brains of psychotic patients.[5] Elevated CK can be seen in brain injury such as cerebrovascular accident, encephalitis, tumor or subdural hematoma. Interestingly, CK-MM is the predominant isoenzyme seen, perhaps because the brain-brain fraction has a brief half-life.

Table 1.
Causes of Elevated Serum Creatine Kinase other than Myocardial Infarction

Hypothyroidism
Skeletal muscle trauma
Intramuscular injection
Seizures
Rhabdomyolysis
Myositis
Muscular dystrophy
Alcohol use
"Psychosis"
Cerebrovascular accident
Encephalitis
Brain tumor
Subdural hematoma

The astute physician must not be lured into making a diagnosis of acute myocardial infarction by a glittering CK on a chemistry profile when any of these other disorders are present.

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Rocky Mountain Spotted Fever in Pregnancy

Harry A. Gallis, M.D., R. Christopher Agner, M.D. and Carroll John Painter, M.D.

IN a recent review of Rocky Mountain Spotted Fever (RMSF) in pregnancy,[1] and in a review of the medical literature through mid-1983, we found no reported clinical experience with RMSF in pregnancy. Since over half of the cases of Rocky Mountain Spotted Fever occur in individuals under the age of 40, it is surprising that it has not been seen in combination with pregnancy. Two of us (RCA and CJP) encountered the following patient in the summer of 1983.

The patient was a 19-year-old caucasian woman in her first pregnancy who noticed and removed an embedded tick on July 31, 1983. Three days later when she was seen at a routine prepartum visit, asymptomatic pyuria was noted, and she was begun on Nitrofurantoin. Five days later she developed a temperature of 101° and her prescription was changed to ampicillin.

Physical examination was remarkable for blood pressure 120/70, pulse 100, mild anxiety, abdominal examination consistent with 34 weeks gestation, and a macular rash over the arms, legs, and upper trunk, with several petechiae on the palms, soles, and upper arms.

The white blood cell count was 8,600 with 58 polys and 20 stabs, with a hemoglobin of 11.5 gms% and a platelet count of 122,000. The electrolytes showed a sodium of 139 mEq/liter, potassium 3.7 mEq/liter, chloride 102 mEq/liter, and CO_2 of 20 mEq/liter. The initial VDRL and Weil-Felix titers were negative.

We diagnosed possible RMSF and started her on intravenous chloramphenicol, 500 mg every 6 hours on August 11, 1983. Within 72 hours she was afebrile. Chloramphenicol was administered by mouth at the same dosage on the 3rd through the 5th day and then was discontinued.

The following acute and convalescent titers for RMSF were obtained:

Dates	*8/12/83*	*8/25/83*
Proteus OX 2	Negative	1:20
Proteus OX 19	Negative	1:640
Proteus OX K	1:40	1:40
Indirect hemagglutination	less than 1:16	1:1,024

These titers are interpreted as diagnostic of acute Rickettsial infection.

Our patient made rapid clinical improvement and completed the rest of her pregnancy, delivering a healthy 5 pound 7 ounce female infant with an Apgar score of 9/9 on September 10, 1983. Complete blood count on the mother at the time of delivery was normal. Complete blood count on the infant revealed a white blood count of 28,300 with 76 polys, 18 lymphs, 5 monos, and 1 Eo. The hemoglobin was 24.7, hematocrit 68, and the platelet count was 161,000. The reticulocyte was 6.6%. The mother and infant were reported well 2 months following delivery.

Rocky Mountain Spotted Fever represents a challenge to the clinician in that diagnosis usually must be made on clinical grounds. In endemic areas such as North Carolina, the two most confounding illnesses are perhaps influenza in the early spring and enteroviral (aseptic) meningitis in the late summer and early fall. Fever, myalgias, and headache may also be early manifestations of other illnesses and may be further confused by the occurrence of skin rash (e.g., measles, infectious mononucleosis, toxic shock syndrome, meningococcemia, other bacteremias, leptospirosis, etc.). The mild CSF pleocytosis that occurs in some patients with RMSF may be equally confounding.

The only specific test for RMSF early in its course is a skin biopsy stained with florescent antibody for *Rickettsia rickettsiae*.[2] This test is positive in over 80% of the cases. If this test is negative or unavailable, patients must be treated empirically depending upon the physician's degree of suspicion of RMSF. Definitive diagnosis therefore must be made by retrospective serology, as it was in our case.

The drugs of choice for all Rickettsial diseases are either tetracycline (30 mg/kg per day in divided doses), doxycycline (100 mg twice daily for the first day followed by 100 mg per day), or chloramphenicol (50 mg/kg/day in divided doses). Since tetracycline and doxycycline are *contraindicated* in pregnancy, suspected or skin biopsy proven cases should be treated with chloramphenicol. Therapy is usually continued for 7-10 days, or for 5 days after defervescence. Blood counts should be monitored every few days during treatment, although adverse effects of chloramphenicol are not usually seen in courses of short duration. Adverse fetal effects may be seen if term delivery is precipitated in the presence of high blood levels.

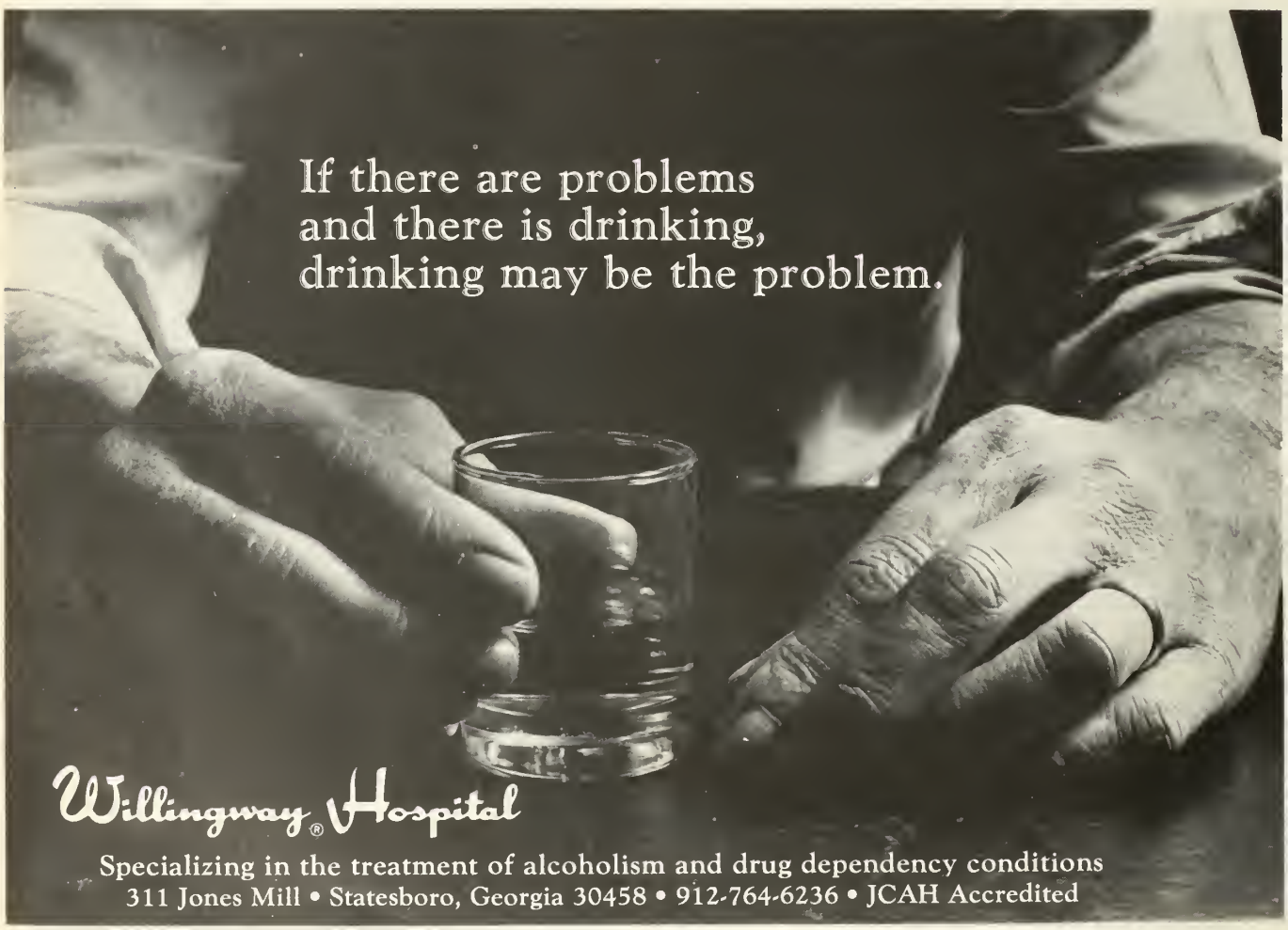
Since there are no previously reported cases of RMSF during pregnancy, one can only speculate as to the potential effects of this infection on the fetus. In severe cases vascular involvement of the placenta could lead to fetal compromise or premature precipitation of labor. A major adverse effect of RMSF might result from its treatment if tetracyclines were inadvertently used during any state of pregnancy. In the first trimester, limb hypoplasia secondary to abnormal osteogenesis may occur.[3] Dentition may be damaged when the crowns of the teeth are developing in the second and third trimesters.[4] In addition, intravenous doses given in the last trimester may cause hepatic failure or pancreatitis in the mother.

On the other hand, chloramphenicol has no more untoward effects during pregnancy than in ordinary use in adults.[5] The drug crosses the placenta in 30-80% of maternal blood levels and there is no known teratogenicity. If given near delivery, however, the gray baby syndrome, a

severe reaction to the drug, may occur. Therefore, this must be weighed against the potential toxicity of tetracyclines or the likelihood of imminent delivery.

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Recent Rulings of the North Carolina Board of Nursing

Hettie L. Garland, R.N.

THE Joint Practice Committee of the North Carolina Medical Society and the North Carolina Nurses Association, in keeping with its objectives to improve communication between nursing and medicine to advance joint planning and action, and to serve as a liaison between the two official parent organizations, requested and received approval from the North Carolina Board of Nursing to regularly publish rulings of the Board that may affect the practice of nurses and physicians in a variety of settings. The North Carolina Board of Nursing regularly publishes the *Bulletin* as a mechanism of disseminating rulings and interpretations as well as other information to registered nurses and licensed practical nurses in the state. However, this information is not always transmitted to physicians and other personnel with whom nurses work. The information contained in this article is excerpted from the *Bulletin* published by the Board of Nursing in September 1983.

The nurse members of the North Carolina Board of Nursing are nominated and elected by the licensees in the state. In addition, two public members are appointed by the Governor. The current membership of the Board follows:

R. Leigh Andrews, RN, Chapel Hill
Sarah Pike Brown, RN, Raleigh
Joyce M. Gainey, RN, Winston-Salem
Olga C. Hoskins, RN, Lenoir
Susan M. Kennerly, RN, Concord
Sharon T. Sells, RN, Stanfield
V. Elizabeth Berryhill, RN, Greenville
Ernestine B. Small, RN, Greensboro
Russell E. Tranbarger, RN, Greensboro
Nancy V. Cook, LPN, Mocksville
Sammy K. Griffin, LPN, Burlington
Christine G. Jones, LPN, Chapel Hill
Betty H. Hunt, LPN, Asheboro
Donna S. Thigpen, Public Member, Beulahville
Joseph H. Nanney, Public Member, Clyde

The following are actions of the Board at the September 1983 meeting:

1. ruled that the removal of suction wound drains upon the order of a physician is within the scope of nursing practice for registered nurses and licensed practical nurses.
2. ruled that the insertion of enteral feeding tubes and other tubes with mercurial bulbs is within the scope of nursing practice.
3. ruled that the insertion of intravenous catheters of lengths no longer than 1½ inches is within the scope of nursing practice for a licensed practical nurse.

In addition, the Board ruled that the following are within the scope of nursing practice for a registered nurse and/or a licensed practical nurse provided that the Board of Nursing has been notified that there is 1) a written protocol, 2) documentation of appropriate training and supervised clinical practice, and 3) written approval of nursing administration, agency administration, and medical staff within the agency:

1. bimanual pelvic and rectal examination is within the scope of practice for a registered nurse.
2. insertion of fetal scalp electrodes is within the scope of nursing practice for a registered nurse when the membranes are ruptured spontaneously or by a physician.
3. removal of a thoracotomy tube is within the scope of nursing practice for registered nurses and licensed practical nurses.
4. administration of subsequent doses of epidural anesthesia is within the scope of nursing practice for a registered nurse.

The North Carolina Board of Nursing celebrated its 80th anniversary on March 3, 1983. North Carolina has the distinction of being the first state to provide for the registration of nurses: on March 3, 1903, then Governor Charles B. Aycock signed the bill establishing the Board of Examiners of Nurses. Over the years since 1903, the statute has been amended and revised. The current nursing practice act became effective July 1, 1981. North Carolina also has the distinction of being the only state that provides for the nomination and election of its nurse members by the licensees in the state.

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Build A "Beta" Mousetrap — Propranolol Poisoning

Ronald B. Mack, M.D.

FOR Heaven's sake why do we need beta blockers — can't we just leave the betas alone!! Almost everything we read today is negative, e.g., starch blockers, field goal blockers, alpha blockers and of course beta blockers. Are "betas" so bad that we have to block them?

Well, it's a long story, but it's basically a lesson in communication. In any good communication system there should be a *sender* and a *receiver* (AKA receptor). Motor nerves communicate information/instructions from the nerve action potential (sender) to the effector, e.g., cells, muscles, nerves, or glands (receptor), via chemical transmitters. These chemical transmitters can affect the receptor in several ways, i.e., as agonists, partial agonists, blockers, or no measurable effect. The *agonist* has an affinity for the receptor and its purpose is to cause the effector cells to do what they do best; to perform in their characteristic fashion. A *blocking agent* also has an affinity for the receptor but does not cause the receptor cells to do their "number." Is this getting too muddled? Look, it is really quite simple. Let me give you an example: I walk into a restaurant in the North End in Boston and my nasal *sensors* pick up the odor of linguine with white clam sauce. I am *agonizing* to receive this delightful dish. My neurotransmitters are really excited — I am salivating, my heart rate increases, my pupils get large, but there is a long line of fellow trenchermen and trencherwomen ahead of me — I am *blocked*.

The peripheral nervous system has two main transmitters that we know about: (1) *acetylcholine* — nerves using this chemical are called cholinergic, (2) *catecholamines* (e.g., norepinephrine, epinephrine, dopamine and isoproterenol) — nerves using these compounds are called *adrenergic*. The adrenergic receptors are further classified into *alpha* and *beta* types. Alpha receptors are primarily excitatory and their stimulation produces vasoconstriction, decreased GI motility, pupillary dilatation, "gooseflesh" and uterine contraction of the gravid uterus (only in women). The *beta receptors* are what we are about in this exercise. They are mainly inhibitory and are found in the heart, blood vessels, GI tract and bronchi. There are two beta receptors that we are concerned about: *beta-1 receptors* predominate in the heart and stimulation of these receptors causes tachycardia, an accentuation of AV conduction and cardiac contraction, thus positive chronotropic (rate) and positive inotropic (force) action. *Beta-2 receptor* stimulation causes vasodilatation, increased GI motility, bronchodilatation, glycogenolysis and hyperglycemia. Well then, *beta blockers* should reverse these effects. Beta-adrenergic blockers are simply competitive inhibitors of catecholamine binding at beta-adrenoreceptor sites. They decrease the effect of a catecholamine agonist on a sensitive receptor tissue. (The cheerleaders now begin the familiar chant — "Block those betas," etc.)

Propranolol (Inderal) is the potential toxin that is the real reason behind this use of lengthy explanations. This drug is one of the most popular of written prescriptions in the United States. Because of its widespread availability overdoses are relatively common. There are plenty of beta blockers on the market but this discussion will be limited primarily to propranolol overdose. Propranolol is a nonselective beta blocking agent, i.e., it blocks both beta-1 and beta-2 receptors (I love it when a drug is not prejudiced). It is currently being prescribed for the amelioration of hypertension, thyrotoxicosis, arrhythmias, angina pectoris, hypertropic subaortic stenosis as well as the prevention of common migraine headaches. Many physicians use this drug in the treatment of severe overdose situations such as with phenylpropanolamine, cocaine or PCP intoxications where hypertension and cardiac arrhythmias are often very troublesome.

Speaking of pharmacokinetics (who brought that up?), propranolol (Inderal) is a weak base with a pKa of 10.4, is 93% protein bound with an apparent volume of distribution of 3.6 l/kg (well, that pretty well eliminates any thoughts of dialysis in overdose situations!). This drug is quite lipid soluble; so much so that it rapidly crosses the blood brain barrier and accumulates in the brain. Propranolol is quite rapidly absorbed from the GI tract. When taken orally about 90% or more is absorbed, but probably only 30% reaches the systemic circulation because the liver exacts a tribute via first pass hepatic elimination. The liver, in fact, almost completely metabolizes Inderal (99%); the rest is eliminated by the kidney. In patients with normal kidney function the peak serum concentration is reached in 1-3 hours whereas the T½ is 2-3 hours in patients who have normal liver function. However, it must be emphasized that in an acute oral overdose situation the T½ may be prolonged.

I suppose that now that we know what beta-1 and beta-2 stimulation produces and also what the blockers (AKA antagonists) do we should be able to figure out what an overdose of propranolol produces in the patient. (Maybe you can; I cannot, so let us proceed.) Adverse clinical

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features following an acute oral overdose can appear in as early as 20 minutes post ingestion but more typically occur in 1-2 hours. There does not appear to be a great deal of clinical correlation between the serum propranolol concentration and its effects on the patient; however, serum concentrations > 1500 ng/ml often are associated with big trouble and concentrations > 14,000-28,000 ng/ml have been associated with fatal outcome. The *two main features* of a large propranolol overdose are *hypotension* and *bradycardia* but *low cardiac output failure* and *cardiogenic shock* are very real possibilities. Needless to say, the patient's before-ingestion cardiac status is an important variable in the assessment of an overdose. It is not too difficult to imagine a person with heart disease (and who has a propranolol supply) becoming depressed and taking a whole bottle of this stuff. In patients with underlying cardiac disease *pulmonary edema* is another real possibility. The patients with pre-existing bronchospastic disease are apt to experience a fair amount of *bronchospasm* following Inderal overdose. *Coma, convulsions* and *respiratory depression* can also occur. In my opinion, one of the most interesting clinical features of propranolol overdose is *hypoglycemia*. It is known that this drug has the ability to interfere with the glycogen mobilizing effects of catecholamines. Apparently this hypoglycemic potential is a problem limited to children and probably diabetics.

In the management of a patient with a propranolol overdose in terms of severity a good history and physical are a must. The EKG findings can vary from a 1st degree AV block (↑ P-R interval) and sinus bradycardia to a complete disappearance of P waves, QRS widening (intraventricular conduction defects) and an old nemesis, asystole. A chest x-ray can reveal the presence of pulmonary edema. It would be wise to order blood glucose and serum potassium levels (hyperkalemia can be reported in some of these patients).

In our experience with the propranolol overdose situation most of the patients require rather careful observation but not much more; maybe we have been lucky so far. As in dealing with other potentially lethal toxins expect the worse but *only treat the patient not the poison*. As a general rule, the commonest causes of death in victims of *any poison* are cardiopulmonary in origin whether secondary to the direct effects on the circulation and lungs or secondary to CNS effects. Therefore, it is no surprise that the principal complications are arrhythmias, hypotension, shock and pulmonary edema. As we have seen, propranolol can produce all of these evil conditions if consumed in excess.

Following an acute overdose, gastric emptying should be performed followed by the administration of activated charcoal and a saline cathartic. *Hypotension* can be caused by the bradycardia or from the depression of myocardial contractility or a CNS effect. If the hypotension is severe enough to require treatment, place the patient in the Trendelenburg position and administer fluids if they are indicated. If there is *sinus bradycardia and hypotension, atropine* seems to be the treatment of choice. If the atropine fails, *isoproterenol* is the next drug to use. Isoproterenol is often required in rather large doses because of the competitive blockade with the beta blocker. Some authors would use dopamine here if the systemic vascular resistance was low and would use dobutamine if the systemic vascular resistance was normal or high. Intracardiac pacing can also be tried. Apparently in *sinus bradycardia without hypotension* no specific treatment may be necessary; it all depends on whether the cardiovascular status is impaired or not. *Convulsions*, other than those caused by hypoglycemia, usually respond to intravenous diazepam (if diazepam fails, give phenytoin).

Glucagon appears to be able to play a decisive and fascinating role in the management of severe propranolol overdose. Glucagon, because it acts at a site quite distant from the beta receptor, activates myocardial adenyl cyclase thus stimulating cyclic AMP synthesis and resulting in cardiac effects similar to beta-adrenergic agonists. Simply stated, glucagon can increase myocardial contractility and heart rate (inotropic and chronotropic effect) despite high circulating concentrations of beta blockers. The effects of a single dose of this drug can produce a dramatic response in 5-10 minutes lasting for 15-30 minutes; if it works in your patient you may want to begin a constant infusion (watch out for emesis and hyperglycemia). Obviously if the patient is hypoglycemic intravenous glucose is the order of the day.

Because so little of the parent drug is excreted unchanged in the urine (less than 1%) forced diuresis is not a good idea and this method can also overload the cardiopulmonary apparatus. The large amount of protein binding and volume of distribution of 3.6 l/kg sort of eliminates the use of dialysis to rid the body of this drug. It is quite encouraging to note that although severe propranolol overdose situations can and do occur, most of your patients will only require gastric decontamination and monitoring.

At the request of the women in my family — a considerable number I might add — my grandson and I are experimenting with the possibility of discovering *theta blockers*. Both he and I suffer from *SMD* which we believe is caused by stimulation of *theta agonists*. SMD is Selective Male Deafness. In this disease certain sounds of specific decibel and frequency emitted by the female voice (grandmother, mother, wife, sister, daughter, colleagues, etc.) are selectively not heard. It can be a devastating illness and has millions of sufferers in this country.

What State Societies Are Talking About: The Resolutions Presented to the AMA House of Delegates at the December 1983 Meeting

Resolutions

1. Nursing Homes — Quality of Care, Medical Staffs and Ancillary Personnel
2. Development of National Policy for Immunizations and Vaccine Development
3. Use of the Choke and Sleeper Holds in Prisons
4. Scientific Accuracy in Racial, Ethnic and Religious Designations in Medical Records
5. Restudy of the Selective Draft of Physicians
6. Support of Individualized Medical Care
7. Amendment to IRS Code to Extend to Physician-Owned Mutual Protective Trusts the Same Tax Benefits as Physician-Owned Liability Insurance Companies
8. Contract Arrangements
9. Reimbursement Systems for Physicians Services
10. Life-Sustaining Medical Treatment (Constitution and Bylaws)
11. Physician Conflict of Interest (Constitution and Bylaws)
12. Regulation of Self-Insured Medical Plans
13. Cessation of Vaccination Program for Smallpox
14. Status of House Speaker and Vice Speaker (Constitution and Bylaws)
15. Preserving the Physician/Patient Relationship (Constitution and Bylaws)
16. Sale of Donor Organs for Transplant (Constitution and Bylaws)
17. Physician Training for Management of Injuries Encountered in Nuclear Explosions
18. Equity in Tax Exemption
19. Patient Medication Instruction (PMI) Sheets
20. "Opium" Perfume
21. Formaldehyde in Manufactured Housing
22. AMA Election Process — Campaign Expenses
23. Care of Handicapped Newborns in Hospitals
24. Poison Control Centers: Computer Linkage for the Dissemination of Information
25. A Mechanism to Correct the Current Discrimination Against Children in Health Insurance
26. Updating of Veterans Administration Rating Schedule
27. Prospective Reimbursement of Hospitals (DRGs) — Ethical Implications (Constitution and Bylaws)
28. Use of AMA CPT-4 by HCFA
29. Organized Self-Governing Medical Staff
30. Prohibition of Military Physicians Serving in Managerial and Administrative Positions
31. 500 Gram Determination for Fetal Births
32. Medicare Preauthorization Review
33. Affirmation of Pledge to Reduce Deaths and Injuries Caused by Drunk Driving
34. Free Competition in Medicine
35. Therapeutic Substitution
36. Peer Review of Medical Fees
37. Publicizing AMA Position on Bioethical Issues (Constitution and Bylaws)
38. Physician Participation in Preferred Provider Organizations
39. Mandatory Medicare Assignments
40. Prospective Payment for Medicare Medical Services
41. Commendation of Motor Vehicle Manufacturers Association, et al.
42. Public Health and Safety Awareness
43. State Society Medical Staff Sections
44. AMA House of Delegates Procedures
45. JCAH Medical Staff Standard
46. Implementation of Smoke Free Society by the Year 2000 within the AMA
47. Development of a Medicare Prospective Payment Pilot Program for Physicians
48. Low Level Radioactive Waste Disposal
49. Direct Advertising of Prescription Drugs to the Public by the Pharmaceutical Industry
50. The Immediate Emergency Care of Critically Wounded Military Servicemen

"Adequate Benefits" in Employer-Offered Health Services

I always enjoy reading the papers submitted by the Council on Medical Services to the House of Delegates. The report on "Adequate Benefits" in Employer-Offered Health Insurance is of interest to all doctors. The Council recommends that an employer would be entitled to take premium payments as a tax deductible business expense only if his health insurance programs provided these "adequate benefits." In order to be judged an "adequate benefits" plan and qualify for tax deduction, the plan would have to meet only two basic requirements:

(a) It would have to provide some extent of coverage for all services listed in Appendix A.
(b) It would have to limit the beneficiary's cost-sharing for covered expenses to a specified maximum of $2,300/person, with this amount updated yearly.

Appendix A
Insurable Health Expenses

A. *Diagnostic, Therapeutic or Preventive Medical Services Provided by or Under Direction of Licensed Physicians in the Office, Hospital, or Other Setting*
   1) Diagnosis and Medical or Surgical Treatment of Illness or Injury
   2) Psychiatric Care
   3) Diagnostic X-ray and Laboratory Services
   4) Radiation Therapy
   5) Consultation
   6) Pre- and Post-Natal Care of Mother and Infant, including delivery
   7) Periodic Medical Examinations: 6 visits per dependent per year for first year of life, biannually for ages 2-21, every 5 years for ages 22-40, every 2 years for ages 41-65
   8) Immunizations Which Are Cost-Effective for the Beneficiary Group Covered

B. *Emergency and Outpatient Services for Physical and Mental Illness*
   1) Outpatient diagnostic services (x-rays, lab tests, etc.)
   2) Use of operating, cystoscopic, cast rooms and supplies
   3) Use of emergency room and supplies for emergencies
   4) Ambulance services
   5) Treatment for alcoholism

C. *Inpatient Hospital Care for Physical and Mental Illness*
   1) Bed, board and nursing services
   2) Drugs, oxygen, blood, biologicals, supplies, appliances and equipment used in the facility
   3) Operating, delivery, recovery room charges; intensive, coronary, special care, rehabilitation unit charges
   4) Diagnostic services (x-rays, laboratory tests, EKGs, etc.)
   5) Care for pregnancy and complications
   6) Physical, occupational, speech therapy

D. *Inpatient Skilled Nursing Facility Care for Physical and Mental Illness*
   1) Bed, board and skilled nursing
   2) Physical, occupational, speech therapy
   3) Drugs, biologicals, supplies or equipment used in the facility

E. *Home Health Services by a Certified Home Health Agency as Ordered by a Physician*
   1) Nursing care
   2) Physical, occupational, speech therapy
   3) Medical supplies and appliances (other than drugs and biologicals)
   4) Rental of durable medical equipment
   5) Oxygen, blood, biologicals

The Council believes that this approach has several major benefits: (1) it allows easy comparability of policies against the standards; (2) rather than attempting to come up with a "laundry list" specifying the amount of each service to be covered, it permits the buyer and seller to negotiate the extent of coverage for the required services — while requiring *some* extent of coverage for all of them and setting a limit on the beneficiary's cost-sharing for covered expenses; and (3) it presents an approach with which the insurance industry is familiar and for which premiums can be determined without significant difficulty.

The Council discusses the standards for adequate benefits under four headings:

Standards for "Adequate Benefits"

1) The plan would provide some extent of coverage for all of the health services listed in Appendix A.
2) Some degree of beneficiary cost-sharing for covered expenses would be required up to a specified per-person limit beyond which no further beneficiary cost-sharing for covered expenses would be required. The cost-sharing limit would be the same for all subscribers and should be set at 10% of the national median family income rounded to the nearest $100 — and updated yearly. Based on current data, the per-person cost-sharing limit would be $2,300.
3) There would be no maximum limit — either lifetime or per episode — on the amount paid by the plan for covered expenses in the catastrophic portion of coverage.
4) In paying for physicians' services, the amount allowed toward meeting the beneficiary's cost-sharing limit would be the difference between the plan payment and the 90th percentile of physicians' customary or median charges in the area (the amount which would cover the customary or median charge for a service at least 90% of the time it is performed). Once the cost-sharing limit was reached, the plan would pay the 90th percentile of customary charges in full. The plan would continue to pay for hospital expenses on a service basis, with contractually specified beneficiary cost-sharing being applied toward the cost-sharing limit.

Cost

The estimated annual premium costs for a plan meeting these adequate benefit standards (coverage for the services specified in Appendix A and a cost-sharing limit) are displayed in Appendix B. These estimates are approximate, and are derived from discussions and information provided by the health insurance industry. They do not represent firm quotations or commitments by any plan or company to offer programs within the price ranges as shown. They are displayed only because they do illustrate for the House that the level of benefits recommended is neither overly expensive on the one hand, nor dangerously lower than the level of protection now commonly provided in employer-offered plans on the other.

As indicated in the Appendix, premium costs will vary with three factors.

1. *Geographic location:* Premium levels will reflect general differences in cost of living and medical care prices from one region to another. Accordingly, premium estimates are given for highest- and lowest-cost areas as well as for the midpoint of that range.

2. *The manner in which the cost-sharing limit is reached:* Premium costs for a plan with a given cost-sharing limit will vary depending on what combination of deductibles and coinsurance is used to reach that cost-sharing limit.

Premium costs will be lowest when the beneficiary pays the entire cost-sharing limit as an up-front deductible before plan coverage begins, and higher when the plan shares part of the cost from the beginning. Accordingly, premium estimates are also given for six different deductible/coinsurance combinations.

The Council believes that the deductible/coinsurance configuration in any given plan should be a matter for individual decision by or negotiation between employer, employees and carrier. However, it is expected that the majority of plans purchased would tend toward the low-deductible extended coinsurance approach, such as "Sample Plans" 1 and 2 in Appendix B.

Appendix B

Plan	Estimated Annual Premium; Per-Person Spending Limit						Estimated Annual Premium; Per-Family Spending Limit, Family Policy		
	Individual Policy			Family Policy					
	Low	Mid	High	Low	Mid	High	Low	Mid	High
Sample 1: $100 deductible, 80/20 coinsurance for remaining $2,200	$524	$773	$1,022	$1,435	$1,882	$2,340	$1,903	$2,917	$3,936
Sample 2: $300 deductible, 80/20 coinsurance for remaining $2,000	$504	$699	$958	$1,394	$1,705	$2,238			
Sample 3: $500 deductible, 80/20 coinsurance for remaining $1,800	$462	$640	$876	$1,280	$1,564	$2,051			
Sample 4: $1,000 deductible, 80/20 coinsurance for remaining $1,300	$404	$559	$764	$1,122	$1,370	$1,793	$1,459	$2,257	$2,988
Sample 5: $1,500 deductible, 80/20 coinsurance for remaining $800	$373	$515	$702	$1,036	$1,265	$1,653			
Sample 6: $2,300 deductible, no coinsurance	$344	$503	$662	$787	$1,018	$1,260			

3. *How the cost-sharing limits are applied:* The estimated average premium cost falls a reasonable distance below the $2,100 family and $840 individual employer premium contribution tax cap currently proposed by the Administration and supported by the AMA.

Eugene A. Stead, Jr., M.D.



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All Contraceptives Have Problems: Toxic-Shock Syndrome and the Vaginal Contraceptive Sponge

FOUR reported cases of toxic-shock syndrome (TSS) meeting CDC criteria occurred in late 1983 among users of the vaginal contraceptive sponge (Today*). The first patient, a Georgia resident, developed symptoms on October 16, while using a sponge for the first time. She was 37 days post-partum. The second patient, from Oregon, developed symptoms on November 14 following several unsuccessful attempts at sponge removal that resulted in fragmentation of the product. The third case occurred on November 20 in a woman from California; the sponge had been in place 32 hours and was removed with difficulty. The fourth case, also from California, occurred on December 10 in a woman who had left the sponge in place for 5 days. Patients ranged in age from 20 to 29 years; all were white, non-Hispanic. None was menstruating at the time symptoms developed.

All patients manifested fever, hypotension, diffuse rash, desquamation, nausea, vomiting, myalgias, mucous membrane hyperemia, and vaginal discharge. All were hospitalized and treated with intravenous fluids and antimicrobial agents, and all recovered. Vaginal cultures in every case were positive for *Staphylococcus aureus*.

The Today Vaginal Contraceptive Sponge was introduced to the over-the-counter market in June 1983. This sponge is made of polyurethane impregnated with the spermicide nonoxynol-9 and is intended to provide 24 hours of contraception. The manufacturer (VLI Corporation) estimates that, as of December 1983, 5 million sponges had been used by more than 250,000 women in 24 western and southern states. During clinical trials, the average woman using only this method of contraception used 10 sponges per month. At the time the sponge was licensed, the U.S. Food and Drug Administration (FDA) required that the package insert contain a warning that clinical trials had not been large enough to assess the risk of TSS and that users should seek medical care if symptoms compatible with TSS developed. Instructions for sponge use indicate that it should not be left in place for more than 30 hours.

Following a meeting with FDA representatives on December 16, the manufacturer highlighted the warning on the package insert and placed a similar warning on the outer box.

Women who use contraceptive sponges should read the package insert carefully and follow the manufacturer's directions. Users who experience difficulty removing a sponge and/or sponge fragmentation should consult a physician. Women who have had TSS, particularly if it was associated with the use of a contraceptive sponge or tampon, should also consult a physician before beginning or resuming use of either. Similarly, post-partum women, who may be at increased risk of developing TSS, should seek medical advice before using the contraceptive sponge.

Reported by GA Faich, S Sobel, J Bilstad, National Center for Drugs and Biologics, U.S. Food and Drug Administration, Rockville, Maryland; Respiratory and Special Pathogens Epidemiology Br, Div of Bacterial Diseases, Center for Infectious Diseases, CDC.

Editorial Note: This report of four TSS cases among women using the contraceptive sponge is presented to inform physicians that a potential problem may exist and to encourage the reporting of additional cases. Given the small number of known cases and the potential reporting biases, the risk of TSS associated with contraceptive-sponge use remains uncertain.

All contraception methods, as well as unprotected intercourse, involve risk either from the methods themselves or from unintended pregnancy. The contraceptive sponge is an effective means of contraception, with a failure rate similar to that for diaphragms; thus, the overall magnitude of the health risks associated with contraceptive-sponge use, including TSS, should be compared with the health risks of other methods of contraception and unprotected intercourse.

If one assumes that the four cases reported so far were all attributable to contraceptive sponges, a minimum estimate of the incidence of nonmenstrual TSS associated with sponge use would be 10 cases (95% CI Poisson distribution, 3-20) per year per 100,000 women who use contraceptive sponges as their only method of contraception. (In comparison, five to 10 menstrual cases per year are expected among 100,000 women who use tampons). Current mortality from TSS is 3%; therefore, 0.3 deaths (0.1-0.8) per year would be expected from these 10 cases of TSS among contraceptive-sponge users, in addition to an estimated 1.2 deaths related to pregnancy due to contraceptive-sponge failure. The overall number of deaths (1.5) attributable to contraceptive-sponge use would thus be comparable to the number of deaths associated with the use of other

* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Reprinted from MMWR, Volume 33, Number 4, February 3, 1984.

effective contraception methods (range 0.1-5.2/100,000 women 20-29 years of age, depending on method used) and less than the risk of death from pregnancy among women using no contraception (8.3/100,000 women 20-29 years of age).

Although not included in these calculations, the use of contraception methods other than the contraceptive sponge may also affect the risk of developing TSS. For example, cases of nonmenstrual TSS among diaphragm users have been reported previously, and, to date, 18 definite and five probable cases associated with diaphragm use have been reported to CDC. Conversely, the use of oral contraceptives may reduce the risk of developing menstrual TSS.

Physicians and other health personnel are requested to report all suspected TSS cases to their state health departments, which will forward copies of the reports to CDC. Pending revision of the TSS report form, the method of contraception in suspected cases should be included in the "other information" section of the current form. TSS report forms can be obtained from local and state health departments or directly from CDC (telephone 404-329-3687).

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Raleigh: (919) 872-1848
Wilmington: (919) 799-0655

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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

March 1-8

Review of Clinical Chemistry Seminar
Place: Greenville
Fee: $315
Credit: 46 hours
Info: Mary C. Valand, Continuing Medical Education, ECU School of Medicine, Box 7224, Greenville 27834. 919/758-5200

March 6

"Duke Tuesday"
Place: Durham
Credit: 5 hours Category I AMA
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

March 6-7

"The Least Restrictive Alternative: Programmatic and Management Issues"
Place: Raleigh
Info: 919/966-5463

March 7

Cardiovascular Disease Update
Place: Sanford
Credit: 6 hours Category 1 AMA
Info: R. S. Cline, M.D., Central Carolina Hospital, Sanford 27339. 919/774-4100, ext 394

March 7-10

"Internal Medicine: 1984"
Place: Chapel Hill
Credit: 25 hours Category I AMA
Fee: $250.00
Info: William B. Wood, M.D., 231 MacNider Bldg 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

March 14

Current Concepts in Family Practice
Place: Greenville
Credit: 6.5 hours Category I AMA
Fee: $50
Info: Mary C. Valand, Continuing Medical Education, ECU School of Medicine, Box 7224, Greenville 27834. 919/758-5200, ext 208

March 15-16

"Eighth Annual Cancer Research Symposium"
Place: Chapel Hill
Credit: 11 hours Category I AMA
Info: Mrs. Mimi Minkoff, Cancer Research Center, UNC School of Medicine, Chapel Hill 27514. 919/966-3036

March 18-21

"Improving Residency Rotations: Curriculum Planning and Negotiation"
Place: Rougemont
Credit: 20 hours Catetory I AMA
Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

March 21

Cardiovascular Disease Update
Place: Sanford
Credit: 6 hours Category 1 AMA
Info: R. S. Cline, M.D., Central Carolina Hospital, Sanford 27339. 919/774-4100, ext 394

March 28-31

"Clinical Epidemiology"
Place: Chapel Hill
Credit: 24 hours
Info: Ruth De Bliek, 322 MacNider Bldg. 202H, UNC School of Medicine, Chapel Hill 27541. 919/966-3641

April 8-11

"Administrative Skills: Faculty as Managers"
Place: Rougemont
Credit: 20 Hours Category I AMA
Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

April 10

"37th Annual Medical Symposium: Pulmonary Medicine"
Place: Greensboro
Info: L. S. Slotnick, M.D., 1018 North Elm Street, Greensboro 27401 919/275-7238

April 11-14

"3rd Annual Spring OB/GYN Symposium"
Place: Durham
Credit: AMA, ACOG
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

April 12

"North Carolina Neuro-Ophthalmology Review"
Place: Chapel Hill
Credit: 2.5 hours Category I AMA
Info: Baird S. Grimson, M.D., UNC School of Medicine, Chapel Hill 27514.

April 20-21

"Carolina Ocutome Workshop"
Place: Chapel Hill
Credit: 13 hours Category I AMA
Info: David E. Eifrig, M.D., UNC School of Medicine, Chapel Hill 27514.

April 25

"Current Concepts in Otolaryngology for Primary-Care Physicians"
Place: Chapel Hill
Credit: 6 hours Category I AMA
Fee: $50.00
Info: Harold C. Pillsbury, M.D., UNC School of Medicine, Chapel Hill 27514

April 27

"Biochemistry Symposium"
Place: Chapel Hill
Info: William B. Wood, M.D., 231 MacNider Bldg. 202H, UNC School of Medicine, Chapel Hill 27514 919/962-2118

May 10-11

Infectious Disease Update 1984
Place: Greensboro
Fee: $75
Credit: 11 hours Category I AMA
Info: Fred Levick, Greensboro AHEC, 1200 North Elm Street, Greensboro 27401. 919/379-4025

May 17-19

Floyd W. Denny Alumni Lecture Series
Place: Chapel Hill
Info: Gerald W. Fernald, M.D., Pediatrics, 509 Burnett-Womack Bldg. 229H, UNC School of Medicine, Chapel Hill 27514. 919/966-2085

May 18-20

Pathokinesiology of Cerebral Palsy
Place: Chapel Hill
Info: Darlene S. Slaton, Physical Therapy, C 221H, UNC School of Medicine, Chapel Hill 27514. 919/966-4708

May 25-26

13th Annual Seminar: Gut and Lung Problems in Pediatrics
Place: Durham
Credit: 12 hours
Fee: $60
Info: Alexander Spock, M.D., Box 2994 Duke University Medical Center, Durham 27710. 919/681-3364

May 25

Pediatrics Day
Place: Greenville
Credit: 7 hours
Fee: $55
Info: Mary C. Valand, Box 7224 ECU School of Medicine, Greenville 27834. 919/758-5200

June 1-2

Neurology for the Practicing Physician
Place: Chapel Hill
Credit: 10 hours Category 1 AMA
Info: Colin D. Hall, M.D., Neurology, UNC School of Medicine, Chapel Hill 27514. 919/966-2526

June 6-7

Fellows Symposium
Place: Chapel Hill
Info: John J. Frey, M.D., 231 MacNider Bldg 202H, Chapel Hill 27514.

June 22-23

American Heart Association, North Carolina Affiliate
35th Annual Meeting and Scientific Sessions
Place: Durham

OUT OF STATE

March 4-10

"Sports Medicine"
Place: Snowshoe, WVA
Credit: 20 hours Category I AMA
Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 5-7

"Gold Coast Seminar: Pediatrics"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 8-11

"New Horizons for Psychosomatic Medicine"
Place: Hilton Head, SC
Credit: 20 hours Category I AMA
Info: Joan K. Erpf. 316/379-0191

April 9-11

"Gold Coast Seminar: OB/GYN"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

May 7-9

Gold Coast Seminar: Medicine
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306 Duke University Medical Center, Durham 27710. 919/684-6485

May 30-June 2

AACA 1984 Spring Seminar in Anesthesiology
Place: Hilton Head, SC
Info: Program Director, American Academy of Clinical Anesthesiologists, P.O. Box 11691, Knoxville, TN 37939-1681. 615/588-6279

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine
Place: Sea Level, GA
Info: Mary C. Valand, CME, ECU School of Medicine, Greenville 27834. 919/758-5200

June 4-8

Cornell University Diagnostic Radiology Update Emphasizing Advances in Imaging and Interventional Procedures
Place: Bermuda
Credit: 30 hours Category 1 AMA
Fee: $400
Info: Ann Wold, Gallagher/Wold, Inc., 420 Lexington Ave., New York 10170. 212/986-1277.

June 27-30

Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Credit: 15.5 hours Category 1 AMA
Fee: $350
Info: A. Langen, Dermatology, Box 3135 Duke University Medical Center, Durham 27710. 919/684-6728

Letters to the Editor

Kudos

To the Editor:

I have wanted to write this letter for several months, but the only way to do things (for me) is to do them when they are on my mind.

Within the span of time that you have been editor of the *North Carolina Medical Journal,* it has become one of my favorite journals. Your choices of changes in style, format, and content, plus your personal input, have made it a pleasure to read. Thank you for this service.

W. M. Fowlkes, M.D.
1209 Glendale Drive
Raleigh 27612

To the Editor:

Our staff was very impressed with the blue pages (645-656) appearing in the October 1983 issue (volume 44, number 10) of the *North Carolina Medical Journal.* I feel it would be very valuable to be able to distribute some of these tracts to our patients. I was wondering if it would be possible for the Coastal Eye Clinic to purchase a supply of these.

Cooper Kunkel, M.D.
1411 Tatum Drive
New Bern 28560

The October issue of the Journal *was a particularly successful one, and we are pleased that you have found it useful. Any reader of the* Journal *is free to copy and distribute articles we publish, but we have not yet considered having extra copies of the blue pages printed for distribution. You can purchase extra copies of individual issues for $2 each.*

To the Editor:

Congratulations for producing a beautiful, readable and more interesting *North Carolina Medical Journal.* I just want to tell you that I find your new format more readable, well-rounded and interesting. You are to be congratulated for your efforts. The North Carolina Medical Society is indeed fortunate to have the benefit of your enormous talents and vast experience in producing this top-flight journal.

Please keep up the good work. I look forward to reading your *Journal* now.

Bertram W. Coffer, M.D.
2800 Blue Ridge Road
Raleigh 27619

About Other Letters to the Editor:

To the Editor:

In the December 1983 issue of the *North Carolina Medical Journal* (44:770-771) there was an editorial from Dr. Robert Phillips of Greensboro which I thought was very perceptive and contributed a great deal to the editorial pages. At the end of Dr. Phillips' editorial you invited readers to express an opinion regarding a regular column of this sort. This letter is to heartily endorse such a practice; even if the number of letters received is such that you are not able to provide one with each issue, I think it would be a very valuable forum for physician opinion.

Charles M. Hassell, M.D.
Moses H. Cone Memorial Hospital
Greensboro 27420

To the Editor:

This letter is in reference to the letter by Dr. Claude A. Frazier, M.D., about Uniform Donor Cards [NCMJ 44:827 (December 1983)].

Since 1950, almost 250,000 North Carolinians have signed donor cards from the North Carolina Eye & Human Tissue Bank, Inc. willing their eyes, any needed parts, and their bodies for anatomical study. About 8,500 pairs of eyes have been retrieved and used by ophthalmologists in North Carolina. Our affiliation with other organ procurement centers in the state has provided other tissues and vital organs.

The North Carolina Eye & Human Tissue Bank, Inc. now has two satellite programs: the Triangle Area (Duke, VA, and N.C. Memorial Hospitals) and Charlotte Memorial Hospital.

The North Carolina Eye & Human Tissue Bank, Inc. has had an exhibit every year for the past thirty-three years at the annual North Carolina Medical Society Meeting.

All of the ophthalmologists who have served and are serving on the Regional Board of Directors have done so free of charge.

In thirty-three years there has NOT been an article about the North Carolina Eye & Human Tissue Bank's activities of supplying corneal and scleral tissue to ophthalmologists for North Carolina citizens. We would appreciate an article in the *Journal* about N.C. Tissue Donation and Retrieval.

L. Byerly Holt, M.D.
3195 Maplewood Avenue
Winston-Salem 27103

The editor will poke his colleagues.

Carolina History

To the Editor:

I have thoroughly enjoyed the papers on North Carolina medical history and I have just written George Harrell a note acknowledging his beautiful commentary entitled "The Early Years at Bowman Gray." I had heard many of the important features of his pioneering work there, and his comments have placed it all in appropriate perspective. He is deserving of so much credit for such a wide array of contributions, and I simply could not be more pleased than by the fact that this was fully recognized when he received an honorary degree from Duke at Commencement.

David C. Sabiston, Jr., M.D.
Duke University Medical Center
Durham 27710

About the Blue (Yellow) Pages

To the Editor:

In talking with Marguerite Tracy recently, she made the excellent suggestion that the new "blue section" (now yellow) of the *North Carolina Medical Journal* would be an excellent medium for emphasizing and informing our physicians about the increasing importance and some of the differences of practice in an older population — and the section might also serve as a tear-out for medical information geared, like the Harvard Medical Letter, to the layman.

It is good to have you use your experience and expertise to inject new life and new usefulness into our state *Journal*.

Monroe T. Gilmour, M.D.
1300 Baxter Street
Charlotte 28204

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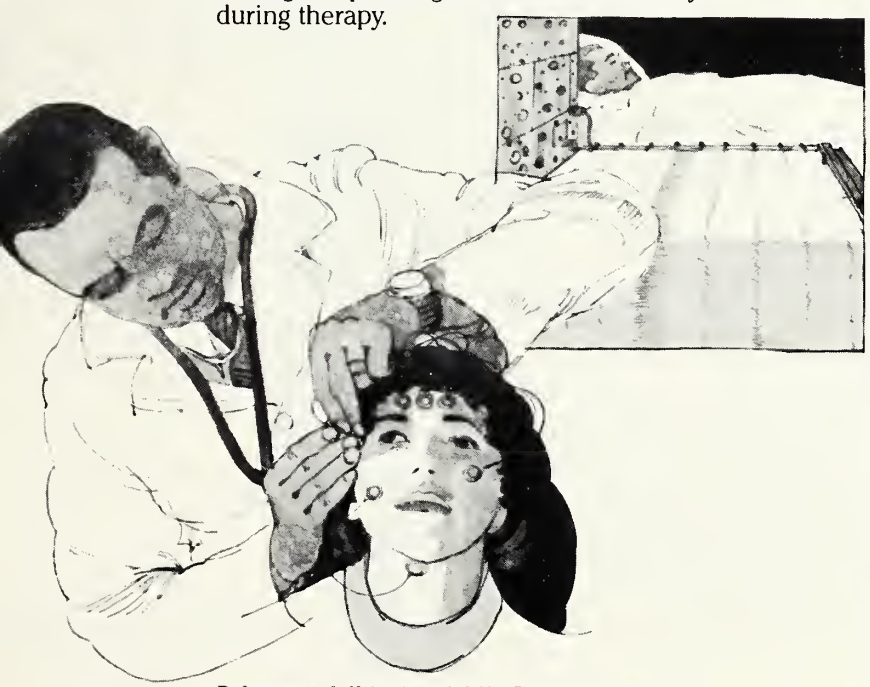
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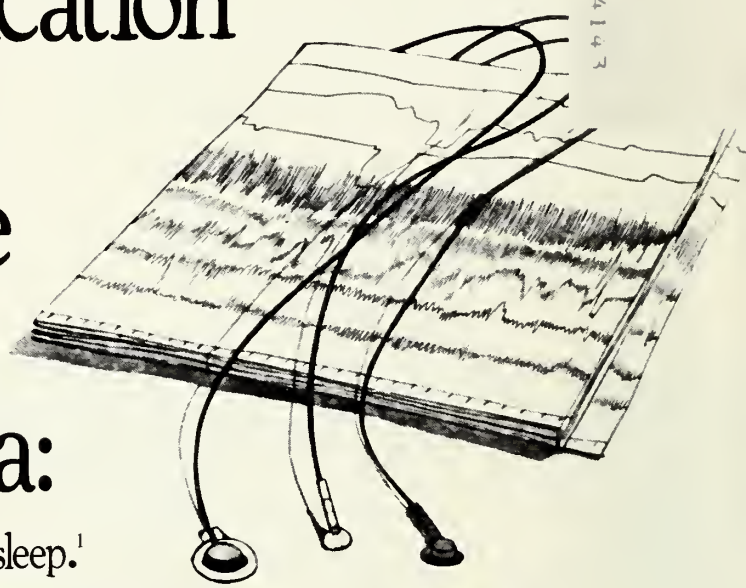
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by David B. Matchar, M.D., C. Edward Coffey, M.D., and John R. Feussner, M.D.

An elderly man with pain in his calf also had sudden vision loss caused by a cholesterol embolus (right arrow) with a cotton wool spot (left arrow) and an area of retinal pallor indicating infarction

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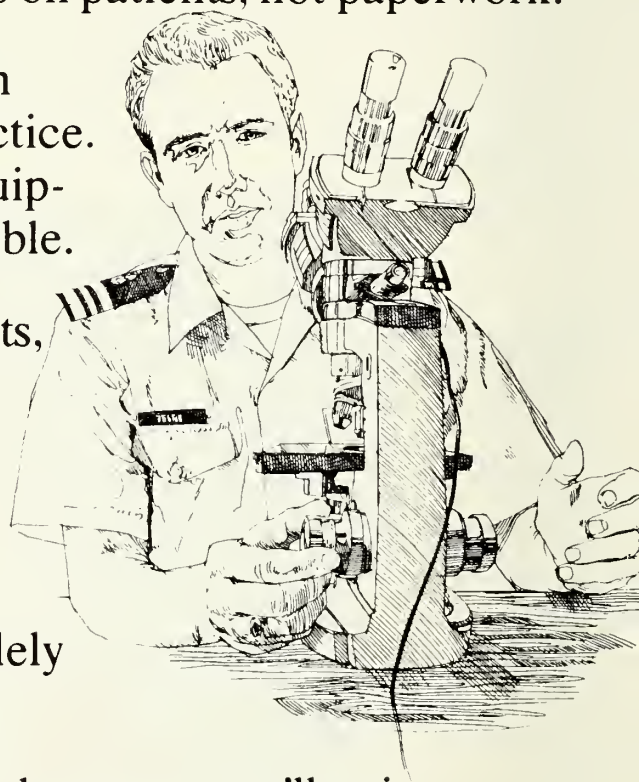
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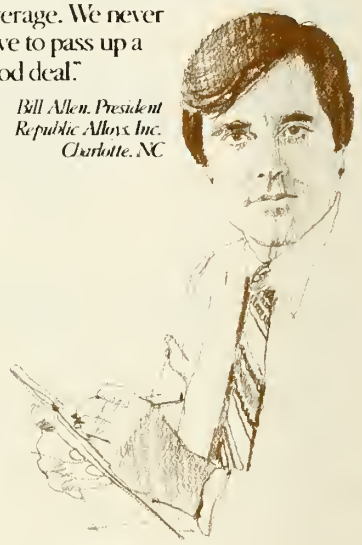
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SCIENTIFIC ARTICLE

Late Reporting of Sudden Vision Loss

David B. Matchar, M.D., C. Edward Coffey, M.D. and John R. Feussner, M.D.

SUDDEN loss or change of vision is an obvious concern for most people, yet for many elderly individuals visual defects are accepted as part of the aging process. As a result, the elderly often fail to report visual changes or represent them inaccurately.[1] In these patients, directed questioning accompanied by a methodical search for objective information on physical examination is of particular importance. In this report, we present a patient whose visual problem was identified through directed questioning; the anatomic cause of the problem was established on initial ophthalmoscopic examination performed in the clinic.

Case Report

H.J.O. is a 78-year-old man referred to the Durham VA Medical Center by his private physician for evaluation of calf pain. During triage examination he described the sudden appearance one month earlier of a dark red, green or blue spot in his lower visual field which was particularly noticeable when he looked to the left or closed his left eye. He felt well otherwise except for a 1-2 year history of right calf pain brought on after walking a few blocks and relieved by rest. He denied prior episodes of vision loss, weakness, numbness, dizziness, jaw or scalp pain, headache or dysarthria. Current medications included aspirin, 650 mg twice a day, and dipyridamole, 50 mg twice a day.

The physical examination revealed a thin, alert, elderly man. Vital signs were normal: weight 59 kg, blood pressure 130/70 mm Hg, pulse 72 beats/min, regular rate. All peripheral pulses were palpable and symmetrical including those of the distal lower extremities. He had bilateral carotid and femoral bruits and an abdominal bruit. Chest was clear to percussion and scattered rhonchi were heard throughout both lung fields. Cardiac examination was normal and no murmurs or rubs were heard. An S4 gallop was present. Extraocular movements and pupillary responses were normal. A right infero-nasal quadrant visual field loss to confrontation was noted. On ophthalmoscopic examination, no opacities were noted in cornea, lens, aqueous or vitreous. Funduscopic examination revealed an orange refractile cholesterol plaque in the supero-temporal artery of the right eye. There was a diminishing distal caliber of the vessel and a pale retina with cotton wool spots [see cover, low power photograph demonstrating cholesterol embolus (upper arrow), cotton wool spot (lower arrow), and area of retinal pallor indicating infarction]. Formal visual fields were performed, which confirmed the infero-nasal visual defect (fig. 1). A mild refractive error was fully correctable by pin hole. The remainder of the neurologic examination demonstrated only mild generalized wasting and decreased vibration sense over both distal lower extremities. Laboratory evaluation included a normal hemogram and coagulation studies, and an EKG which showed a sinus bradycardia at a rate of 58.

Discussion

The anatomic etiology of visual loss can often be defined through basic maneuvers available to the non-ophthalmologist.[2, 3] The subsequent evaluation is directed at

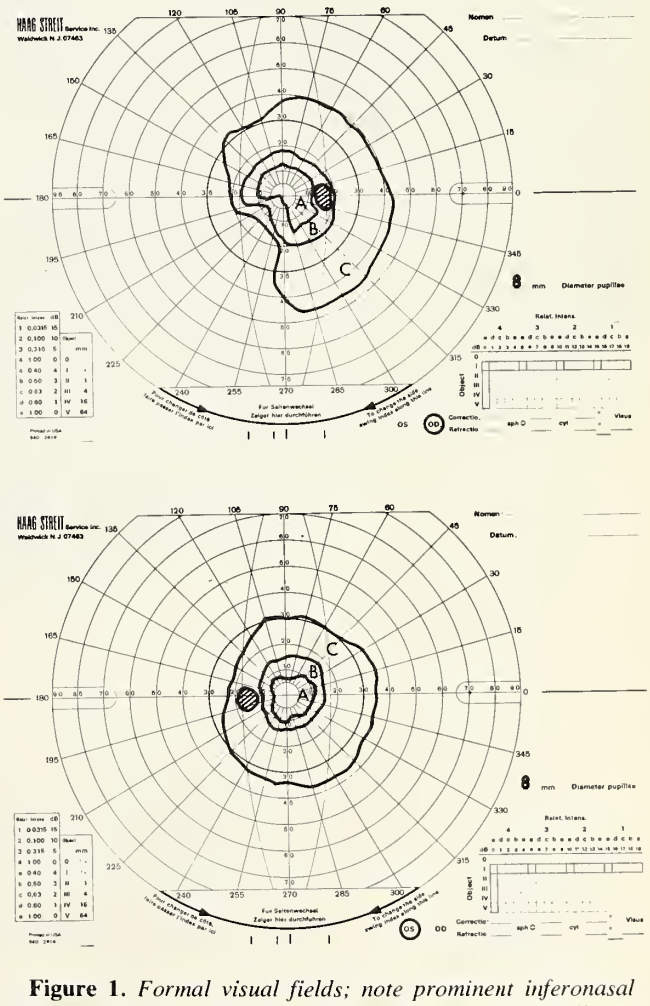


Figure 1. *Formal visual fields; note prominent inferonasal field defect O.D. for all targets. Letters correspond to different colors, sizes and intensities of the targets: A = red, 3 mm, intensity 4; B = white, 1mm, intensity 3; C = white, 1 mm, intensity 4.*

From the Ambulatory Care Section, Durham VA Medical Center and the Divisions of General Internal Medicine and Neurology, Duke University Medical Center, Durham 27710.

establishing the pathologic etiology so that appropriate therapy may be initiated.

Most patients with retinal infarction are presumed to have had embolization of cholesterol, fibrin or platelet aggregates from the internal carotid system to branches of the ophthalmic artery.[4] Perhaps 5% of retinal infarctions[4, 5] are caused by emboli from a cardiac source, for example, subacute bacterial endocarditis, myocardial infarction or valvular disease including mitral valve prolapse. Therefore, a cardiac history and physical examination, supplemented when appropriate by laboratory data (erythrocyte sedimentation rate, blood cultures, EKG, echocardiogram, Holter monitoring), are required in every patient. Other less common causes of retinal infarction include glaucoma, giant cell arteritis, polycythemia and thrombocytosis. Migraine headaches may mimic amaurosis fugax but rarely if ever cause retinal infarction.

If surgery is being strongly considered as a therapeutic alternative, angiography is the most accurate and reliable technique for defining the presence and extent of carotid atherosclerosis in patients with retinal infarction. Noninvasive procedures may have a role in the evaluation of asymptomatic or mildly symptomatic patients, but they do not obviate the need for angiography in the surgical candidate.[6]

Medical treatment of atherosclerosis is limited by our inadequate understanding of its pathogenesis. Anticoagulation and anti-platelet agents have been employed,[7] but only aspirin has been shown to reduce stroke in a satisfactory study.[8]

Surgical treatment is limited by the diffuse character of atherosclerosis as well as the frequency of co-morbid conditions. Removal of the apparently offending lesion or bypass would appear ideal, but data demonstrating efficacy are limited. The only randomized prospective study of extracranial arterial occlusive disease to date indicates that surgical treatment of carotid disease surpassed medical therapy only when the disease was isolated.[9] Unfortunately, as is the case with carotid bruit, retinal infarction is frequently a marker of extensive vascular disease, particularly coronary artery disease.[10] Visible cholesterol emboli themselves bode poorly for patients with retinal infarction as they have been associated with decreased survival.[10]

Course

In view of the patient's age and generalized vascular disease, he was continued on aspirin and dipyridamole without further evaluation. Four months later he was seen by another ophthalmologist. At that time he had had no further neurological or visual complaints. The plaque and field cut remained unchanged. He was referred to a vascular surgeon, who performed carotid arteriography. Bilateral proximal ulcerative lesions with mild stenosis were noted. Endarterectomy was performed on the right carotid artery. There were no apparent complications and the patient was discharged on aspirin and dipyridamole.

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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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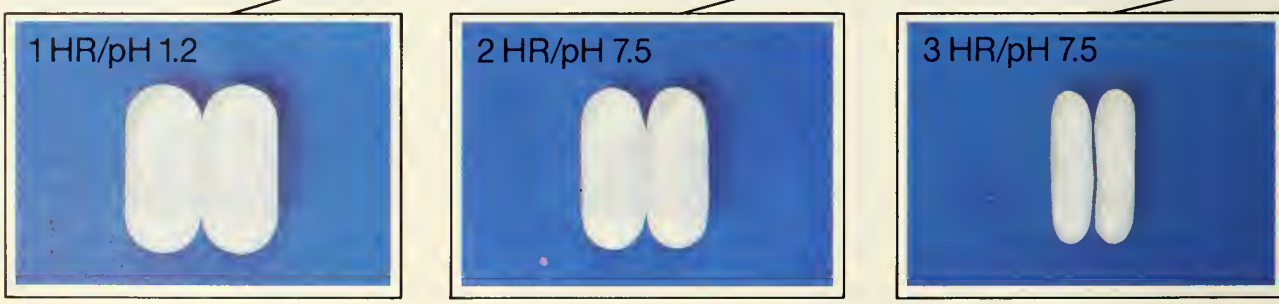
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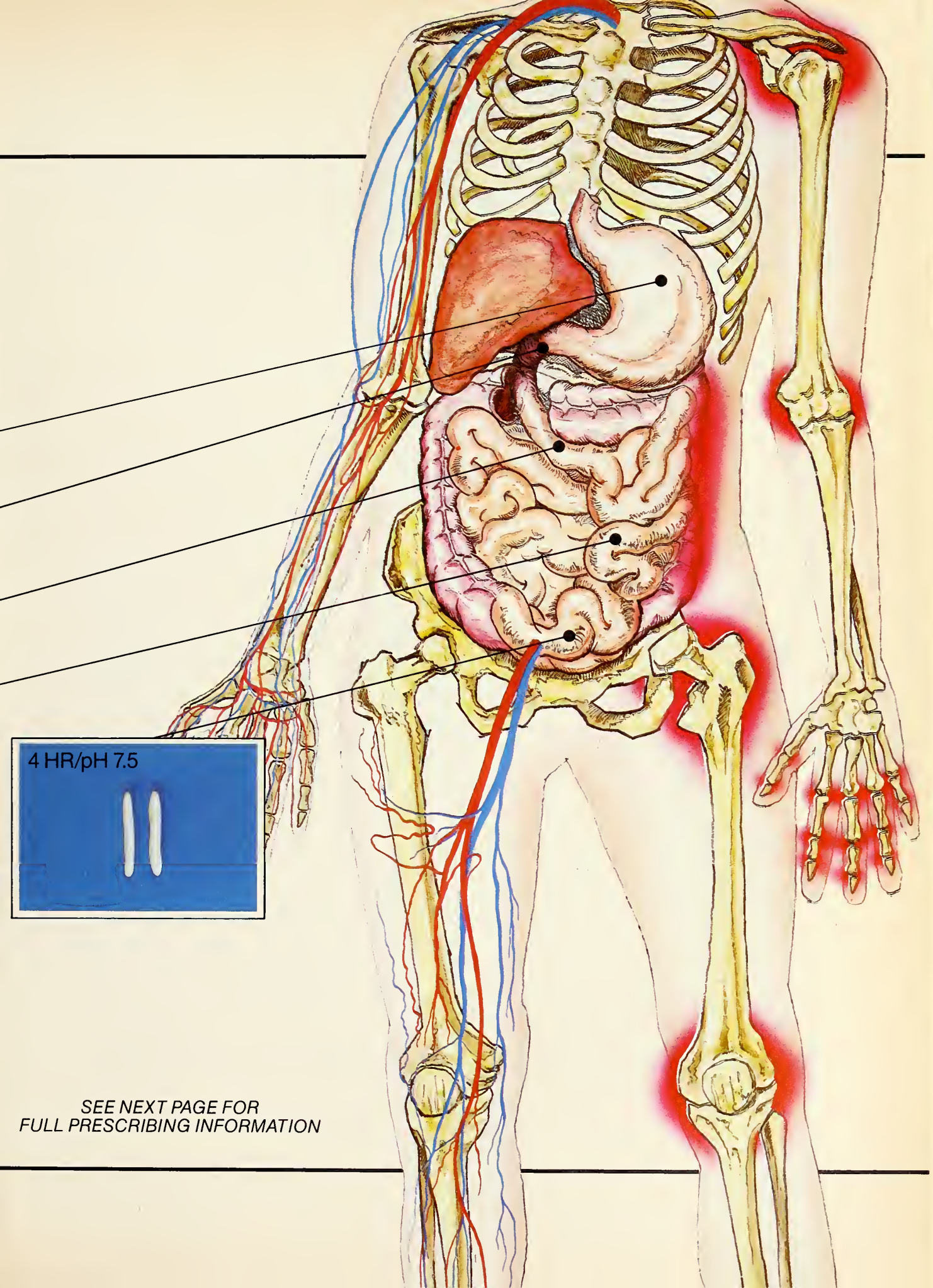


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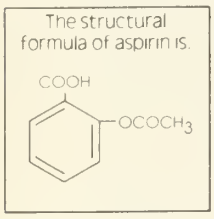
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FULL PRESCRIBING INFORMATION

ZORprin (ASPIRIN) Zero-Order Release

DESCRIPTION: Each capsule-shaped tablet of Zorprin contains 800 mg of aspirin, formulated in a special matrix to control the release of aspirin after ingestion. The controlled availability of aspirin provided by Zorprin approximates zero-order release; the *in vitro* release of aspirin from the tablet matrix is linear and independent of the concentration of the drug. □ **CLINICAL PHARMACOLOGY:** Aspirin, as contained in Zorprin, is a salicylate that has demonstrated anti-inflammatory and analgesic activity. Its mode of action as an anti-inflammatory and analgesic agent may be due to the inhibition of synthesis of prostaglandins, although its exact mode of action is not known. □ Zorprin dissolution is pH-dependent. *In vitro* studies have shown very little aspirin to be released in acidic solutions, whereas, Zorprin releases the majority of its aspirin (90%) in a zero-order mode at a neutral to alkaline pH. It is this pH dependence of Zorprin that reduces direct contact between aspirin and the gastric mucosa, resulting in a reduction of its gastrointestinal side-effect potential. □ Bioavailability data for Zorprin have confirmed that plasma levels of salicylic acid and acetylsalicylic acid can be measured 24 hours after a single oral dose. This substantiates a twice daily dose regimen. Multiple dose bioavailability studies showed similar steady-state salicylate levels for Zorprin as for conventional release aspirin using the same total daily dose. Long-term monitoring of salicylate levels showed no signs of accumulation once steady-state levels were reached (4-6 days). □ Studies of *in vivo* prostaglandin levels (PGE2) have shown Zorprin plasma levels of salicylic acid and acetylsalicylic acid to reduce PGE2 levels 14 hours after a single oral 800 mg dose while an equivalent dose of aspirin produced a reduction of PGE2 levels only through six hours. Zorprin's effect on prostaglandins other than PGE2 has not been determined. □ Salicylates are excreted mainly by the kidney, and from studies in humans it appears that salicylate is excreted in the urine as free salicylic acid (10%); salicyluric acid (75%) salicylic phenolic (10%); acyl glucuronides (5%) and gentisic acid (<1%). □ **INDICATIONS & USAGE:** Zorprin is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of Zorprin have not been established in those rheumatoid arthritic patients who are designated by the American Rheumatism Association as Functional Class IV (incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care) □ In patients treated with Zorprin for rheumatoid arthritis and osteoarthritis, the anti-inflammatory action of Zorprin has been shown by reduction in pain, morning stiffness and disease activity as assessed by both the investigators and patients. □ In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Zorprin has been shown to be comparable to conventional release aspirin in controlling the aforementioned signs and symptoms of disease activity and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS). Zorprin may be well tolerated in some patients who have had gastrointestinal side effects with conventional release aspirin, but these patients when treated with Zorprin should be carefully followed for signs and symptoms of gastrointestinal bleeding and ulceration. □ Since there have been no controlled trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of Zorprin in conjunction with other nonsteroidal anti-inflammatory agents (NSAI), the combination cannot be recommended (see **Drug Interactions**) □ **Because of its relatively long onset of action, Zorprin is not recommended for antipyresis or for short-term analgesia.** □ **CONTRAINDICATIONS:** Zorprin should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema, bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. Zorprin is not recommended for children under 12 years of age, it is contraindicated in all children with fever accompanied by dehydration. □ **WARNINGS:** Zorprin should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress platelet aggregation and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics; concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. □ While salicylates in large doses have a uricosuric effect, smaller amounts may reduce water excretion and increase serum uric acid. □ USE IN PREGNANCY. Aspirin can harm the fetus when administered to pregnant women. Aspirin interferes with maternal and infant hemostasis and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. □ If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. □ Aspirin should not be taken during the last 3 months of pregnancy. □ **PRECAUTIONS:** Appropriate precautions should be taken in prescribing Zorprin for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing Zorprin for those patients with bleeding tendencies or those on anticoagulants. □ In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when Zorprin is made a part of the treatment program. □ Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by dosage reduction. □ Salicylates can produce changes in thyroid function tests. □ Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery. □ Since aspirin release from Zorprin is pH dependent, it may change in those conditions where the gastric pH has been increased as a result of antacids, gastric secretion inhibitors or surgical procedures. □ **Drug Interactions:** (See **WARNINGS**) Aspirin may interfere with some anticoagulant and antidiabetic drugs. Drugs which lower serum uric acid by increasing uric acid excretion (uricosurics) may be antagonized by the concomitant use of aspirin, particularly in doses less than 2.0 grams/day. Nonsteroidal anti-inflammatory drugs may be competitively displaced from their albumin binding sites by aspirin. This effect may negate the clinical efficacy of both drugs. Also, the gastrointestinal inflammatory potential of nonsteroidal anti-inflammatory drugs may be potentiated by aspirin. The combination of alcohol and aspirin may increase the risk of gastrointestinal bleeding. □ Aspirin may enhance the activity of methotrexate and increase its toxicity. □ Sodium excretion produced by spironolactone may be decreased in the presence of salicylates. Concomitant administration of other anti-inflammatory drugs may increase the risk of gastrointestinal ulceration. Urinary alkalinizers decrease aspirin's effectiveness by increasing the rate of salicylate renal excretion. Phenobarbital decreases aspirin's effectiveness by enzyme induction. □ **Pregnancy Category D.** See **WARNINGS** Section. □ **Nursing Mothers:** Salicylates have been detected in the breast milk of nursing mothers. Because of the potential for serious adverse reactions from aspirin in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the benefit of the drug to the mother. □ **ADVERSE REACTIONS: Hematologic:** Aspirin interferes with hemostasis. Patients with a history of blood coagulation defects or receiving anti-coagulant drugs or with severe anemia should avoid Zorprin. Aspirin used chronically may cause a persistent iron deficiency anemia. □ **Gastrointestial:** Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from Zorprin is designed to occur in the small intestine over a period of time. This has resulted in fewer symptomatic gastrointestinal side effects. □ **Allergic:** Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. Fatal anaphylactic shock, while not common, has been reported. □ **Respiratory:** Aspirin intolerance, manifested by exacerbations of bronchospasm and rhinitis, may occur in patients with a history of nasal polyps, asthma, or rhinitis. The mechanism of this intolerance is unknown but may be the result of aspirin-induced shunting of prostaglandin synthesis to the lipoxygenase pathway and the liberation of leukotrienes, *e.g.* slow-reacting substance of anaphylaxis. □ **Dermatologic:** Hives, rashes, and angioedema may occur, especially in patients suffering from chronic urticaria. □ **Central Nervous System:** Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. □ **Renal:** Aspirin rarely may aggravate chronic kidney disease. □ **Hepatic:** High doses of aspirin have been reported to produce reversible hepatic dysfunction. □ **OVERDOSAGE:** Overdosage, if it occurs, would produce the usual symptoms of salicylism: tinnitus, vertigo, headache, confusion, drowsines, sweating, hyperventilation, vomiting or diarrhea. Plasma salicylate levels in adults may range from 50 to 80 mg/dl in the mildly intoxicated patient to 110 to 160* mg/dl in the severely intoxicated patient. An arterial blood pH of 7.1 may indicate serious poisoning. The clearance of salicylates in children is much slower than adults and should receive due consideration when aspirin overdosages occur in infants; salicylate half-lives of 30 hours have been reported in infants 4-8 months old. Treatment for mild intoxication should include emptying the stomach with an emitic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of sodium bicarbonate and dextrose or sodium lactate. In extreme cases, hemodialysis or peritoneal dialysis may be required. □ (*A plasma salicylate level of 160 mg/dl in an adult is usually considered lethal.) □ **DOSAGE & ADMINISTRATION:** *In order to achieve a zero-order release, the tablets of Zorprin should be swallowed intact.* □ *Breaking the tablets or disrupting the structure will alter the release profile of the drug.* □ *It is recommended that Zorprin be taken with sufficient quantities of fluids (8 oz. or more).* □ **Adult Dosage:** For mild to moderate pain associated with rheumatoid arthritis and osteoarthritis, the recommended initial dose of Zorprin is 1600 mg (2-800 mg tablets) twice a day. Because of Zorprin's prolonged release of aspirin into the bloodstream, Zorprin tablets may be taken as a b.i.d. dose. Further adjustment of the dosage should be determined by the physician, based upon the patient's response and needs. Since it will take 4-6 days to reach steady-state levels of salicylic acid with Zorprin, it is recommended dosages be given for at least one week before further adjustment. In general, patients with rheumatoid arthritis seem to require higher doses of Zorprin than do patients with osteoarthritis. □ **Zorprin is not recommended for children below the age of 12.** □ **HOW SUPPLIED: Zorprin Tablets 800 mg;** plain, white capsule-shaped tablets. □ Bottles of 100 Tablets — NDC 0524-0057-01. □ **Caution:** Federal law prohibits dispensing without prescription. □ U.S. Patent No. 4,308,251. □ **Manufactured and Distributed by: BOOTS PHARMACEUTICALS, INC., Shreveport, Louisiana 71106 U.S.A.**



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SCIENTIFIC ARTICLE

A New Era in Pharmacotherapy: The Need to Understand the Principles of Therapeutic Drug Monitoring

Richard H. Drew, RPh.

RELATIONSHIPS between serum drug levels and pharmacologic activity, coupled with increasing pharmacokinetic data, have made therapeutic drug monitoring a reality. This enables the clinician to individualize and optimize pharmacologic treatment while minimizing the risk of drug-induced toxicities. Interpretation and application of serum drug level data, however, require a basic understanding of pharmacokinetic concepts and principles regarding therapeutic drug monitoring. This article presents and reviews concepts such as availability, distribution and clearance, and applies these parameters to the interpretation of serum drug level data.

Although the pharmacologic effect of a drug depends on its concentration at a target organ or cell, this relationship cannot be directly quantitated. However, a correlation between serum drug levels and pharmacologic activity (therapeutic and toxic) may exist for certain agents and could be clinically utilized if both a laboratory assay and sufficient kinetic information existed.

The increase in analytical capabilities, coupled with an explosion of information regarding the pharmacokinetics and pharmacodynamics of drugs, has made the concept of therapeutic serum drug level monitoring a reality. This allows for initiation and modification of therapy based on objective laboratory data when such information is correlated with clinical parameters. This makes it possible to individualize drug therapy, thus maximizing a therapeutic effect while minimizing the risk of side effects and/or toxicity. The interpretation of these data requires a basic understanding of pharmacokinetics. Although this may be perceived by many as the ultimate answer to optimizing all pharmacologic intervention, the applications, capabilities, and limitations of serum drug level monitoring must be put in perspective to best define its therapeutic contribution. This article is intended to discuss basic pharmacokinetic concepts and other principles essential to therapeutic serum drug level monitoring.

Principles of Pharmacokinetics — A Brief Overview

Pharmacokinetics can best be described as the quantitative study of the metabolic processes and relationships between a drug dose and its concentration in biologic fluids.[1] This correlation is the net effect of influences from drug availability, distribution and clearance. Each of these parameters establishes the unique pharmacokinetic profile of a drug and is essential to the interpretation of serum drug level data (see figure 1).

Availability

The availability of an agent for systemic distribution is largely a function of the degree of absorption. A drug's physiochemical characteristics (such as solubility and stability) influence orally administered agents, since the drug must be in solution to be absorbed (often a rate-limiting step) and cannot be chemically broken down by gastric or other body fluids. Product formulations such as sustained-release preparations (both oral and parenteral) often take advantage of solubility properties to delay or prolong absorption, while those already in solution may enhance this rate. Also, since most drugs undergo passive diffusion, only the unionized form can be absorbed. Therefore, oral agents will be dependent on gastric and intestinal pH as well as the pKa of the agent.

Route of administration may affect both the rate and the extent of drug absorption (see figure 2). Orally administered agents usually attain peak serum levels within a few hours after administration. Intravenously administered drugs result in higher, rapid peak serum drug levels, because they are able to bypass the process of passive diffusion and are already in solution. Intramuscular and subcutaneous administration usually yields rapid but lower peak serum levels when compared with the intravenous

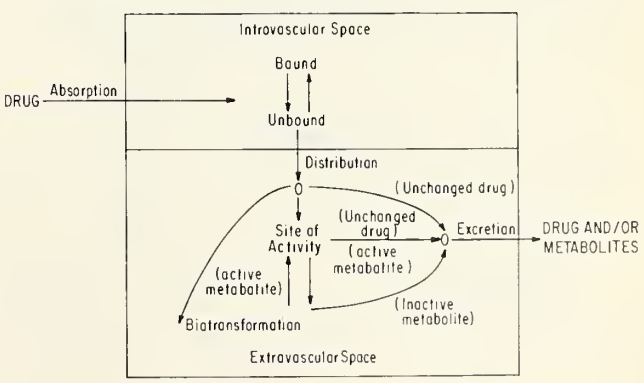


Figure 1. *Drug absorption, distribution, biotransformation, and excretion.*

From the Department of Pharmacy, Duke University Medical Center, Durham 27710.

Table 1
Bioavailability of Digoxin Preparations*[8]

Product	Route of Administration	Bio-availability
Lanoxin Tablet	PO	60-80 %
Lanoxin Elixir	PO	70-85 %
Lanoxicaps	PO	90-100%
Lanoxin Injection	IM	70-85 %
Lanoxin Injection	IV	100%

* Product comparison for the Burroughs-Wellcome digoxin preparations. Substantial bioavailability differences may exist with other products.

route. However, absorption from intramuscular or subcutaneous sites may be erratic for some drugs (such as phenytoin [Dilantin] and diazepam [Valium]).[2, 3]

It must be understood that the extent of drug absorption from a given route is not reflected by the peak serum level (as plotted on the serum concentration vs. time graph). The degree of absorption (known most commonly as bioavailability) is usually expressed as a percentage comparison between the areas under the curve (AUC) of a single dose of a drug via a given route as compared with the same dose administered intravenously (see figure 2). Bioavailability is thus not only dependent on product formulation, but also on route of administration. A good illustrative example would be the bioavailability profile of Lanoxin (see table 1).

Another factor that may influence the availability of a drug administered either orally or rectally is hepatic or gut wall metabolism following absorption, before the drug is circulated systemically. This "first-pass metabolism" may account for substantially larger requirements for oral dosing when compared with intravenous administration to produce comparable serum levels. Propranolol (Inderal) and verapamil (Isoptin) are two examples of drugs that exhibit a high degree of first-pass metabolism.[4, 5]

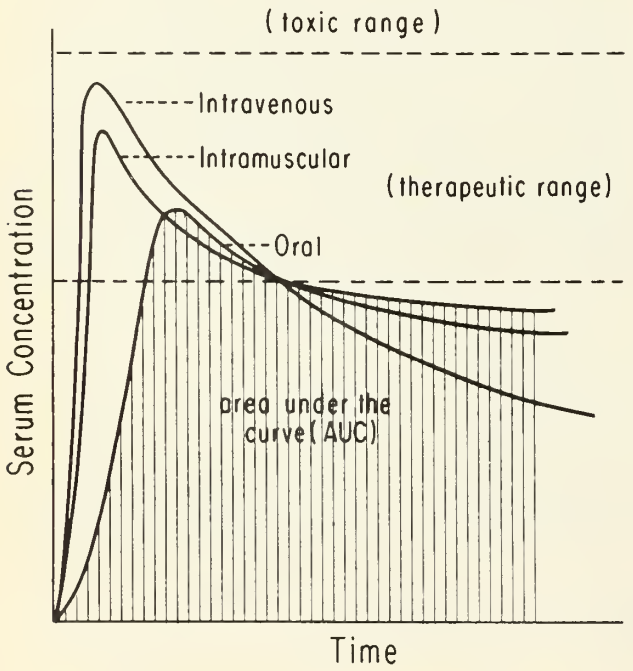


Figure 2. *Absorption profile from various routes of administration.*

The knowledge of a drug's absorption and availability is essential in predicting the time of peak plasma levels or for interpreting laboratory results as either peak, trough or an intermediate value. Factors that influence availability (such as formulation, route of administration, etc.) must be known for the drug and may often be identified by serum drug level monitoring as the cause of a subtherapeutic or toxic response. This information is also essential in modification of a dose when a preparation or route of administration is altered during therapy.

Distribution

Following absorption, the drug undergoes distribution from the intravascular space to various extravascular tissues and fluids (see figure 1). This distribution is best

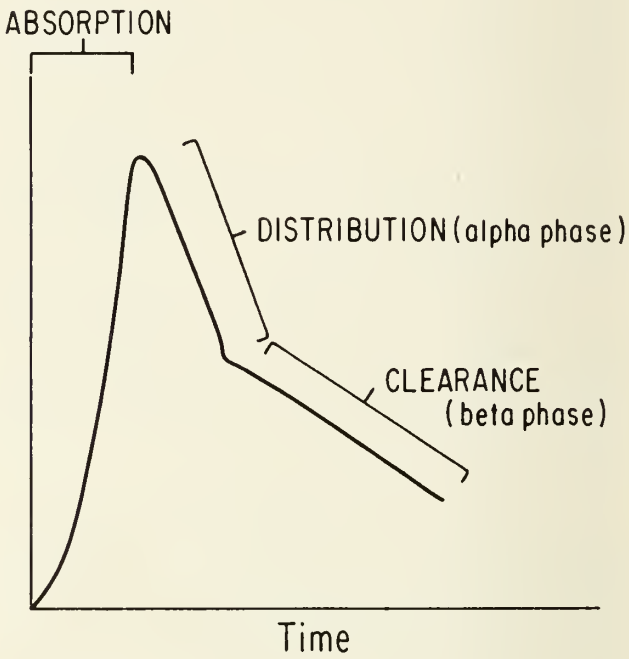


Figure 3. *Illustration of drug absorption, distribution, and clearance following a single oral dose.*

illustrated graphically as the early portion of the declining serum concentration vs. time curve (known as the alpha phase) (see figure 3). If simplified, the body can be pictured as a single compartment for this distribution. A relationship can be established between available drug and the serum levels resulting from its administration. This relationship, known as the volume of distribution, represents a hypothetical volume in which the drug would be distributed throughout to produce a given serum concentration. Expressed in unit volume per unit of weight (L/kg), the volume of distribution does not truly represent a real body space, but rather provides a proportionality constant relating plasma concentrations to total body stores of a drug. Unfortunately, many drugs exhibit "multi-compartment" kinetics which demonstrate different rates of equilibrium.

Binding of a drug to serum proteins will also influence drug distribution. Since drugs bound to serum proteins

(primarily albumin and alpha-l-acid glycoprotein) probably cannot cross membranes, evidence exists that an equilibrium is established between bound and unbound (''free'') drug, and that only this free drug possesses pharmacologic activity. Such binding may therefore vary with the level of plasma proteins. Also, other agents which may compete and thus displace drugs from protein binding sites may result in increases in free (active) drug plasma concentrations. This becomes most significant with drugs that are highly protein bound, since small changes in the bound fraction may result in large alterations in the fraction that is free (see table 2).

The concept of drug distribution and its relationship to serum drug levels is important to understand for several reasons. First of all, blood samples taken while a drug is undergoing distribution may not accurately reflect extravascular tissue or fluid levels if an equilibrium has not been established between these spaces. Therefore, concentrations at the site of activity may be increasing in the face of declining serum levels. Drugs that exhibit multicompartment kinetics cannot be monitored by single serum drug level determinations, since this equilibrium is difficult to predict. Factors that alter plasma proteins or drug binding may influence response without necessarily changing plasma drug levels. This leads us to discuss the fact that laboratory data generated represent total (free and protein-bound) levels, and may not accurately reflect the amount of pharmacologically active (free) drug concentration. It has been postulated that similar therapeutic or toxic responses between patients at differing serum plasma concentrations of drug may be due (in part) to similar free drug concentrations. Capabilities are being developed for many drugs to measure this active fraction and may eventually lead to redefining therapeutic ranges.

Clearance

The clearance of a drug following the absorptive process is the net result of both biotransformation (metabolism) and elimination, and is responsible for determining the agent's duration of activity. It can also be illustrated graphically on the serum concentration vs. time graph and is known as the beta-phase (see figure 2).

Biotransformation of a drug may terminate its activity or lead to the formation of active metabolites, which may then undergo further metabolism or be excreted (see figure 1). Therefore, the terms ''detoxify'' and ''inactivate'' are misnomers. This transformation is due primarily to hepatic metabolism by microsomal enzyme systems to a more water-soluble molecule for excretion and may be influenced by factors altering these enzymes or by affecting hepatic blood flow. Although many agents will be metabolized as a constant percentage of the absorbed drug (first-order kinetics), other drugs will saturate hepatic or other enzyme systems and result in a constant rate of metabolism despite total body levels (zero-order kinetics). Some agents, such as salicylates, may exhibit both first-order and zero-order kinetics, depending on the dose administered. Therefore, changes in the amount of drug administered may produce disproportionate alterations in corresponding plasma levels.

Renal excretion is the primary method of elimination for most drugs and is the net result of glomerular filtration and/or tubular secretion. The parent compound and/or its metabolites (active and inactive) may be excreted in this manner. Other minor routes of elimination may be through sweat glands, lungs, or biliary tract and may become more significant if the principal route is impaired.

Total body clearance of a drug, therefore, is the sum of both metabolism and elimination and represents the rate of drug removal from the body. This rate may also be reflected in the elimination half-life, or the time required for the serum concentration to decline by 50%. Determination of this value may assist in designing the optimum dosing schedule and predicting fluctuations in drug plasma concentrations within a dosing interval.

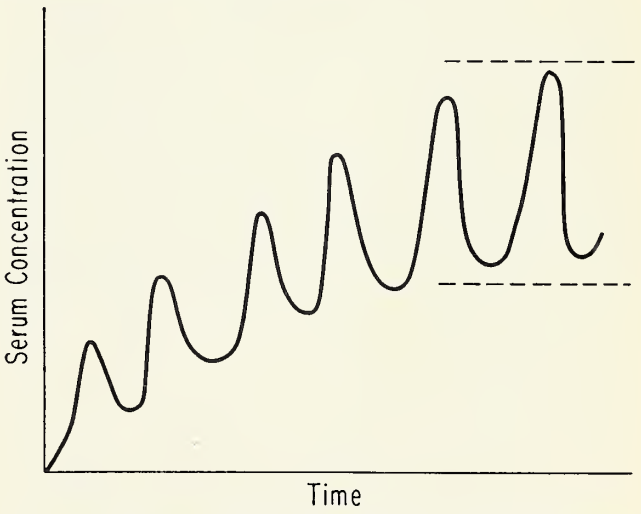


Figure 4. *Establishment of steady state concentrations following repeated dosing.*

Table 2
Effect of a 2% Decrease in Protein Binding of Drugs

	Before		After		
	Fraction Bound	Fraction Free	Fraction Bound	Fraction Free	% Change in Free (Active) Drug
Drug A*	98%	2%	96%	4%	100%
Drug B†	60%	40%	58%	42%	5%

* Drug A represents a highly protein-bound drug
† Drug B represents a moderately protein-bound drug

As the drug is absorbed and continues to distribute into extravascular spaces, fluctuations are seen in both peak and trough concentrations until an equilibrium is reached between administration and elimination. This equilibrium, or steady state, is usually reached after the fifth dose if the interval is close to the drug's elimination half-life (see figure 4).

The knowledge of a drug's clearance is imperative to therapeutic serum drug level monitoring. Although assays will routinely detect parent drug concentrations, the amount or accumulation of pharmacologically active metabolites may become significant in chronic dosing or if elimination is impaired. Routes of metabolism and/or excretion may be influenced by a variety of factors, and should be considered when laboratory data are interpreted. Also, knowledge of a drug's elimination half-life will assist in predicting time to achieve steady state concentrations, since peak and trough levels determined before this equilibrium is reached will be subject to fluctuations. Caution must be used, however, in extrapolating elimination half-life to predicting duration of pharmacologic effect, since many drugs continue to demonstrate activity despite "subtherapeutic levels."

Serum Drug Level Monitoring

Indications

In order for serum drug level monitoring to be effectively utilized, there are several requirements. First of all, a method to assay the compound should be developed and available for clinical use. Sufficient data must then be collected to establish and document a correlation between a pharmacologic effect and serum concentrations. Once these are available the value of serum drug level monitoring must be assessed for its contribution to patient care. Its use should be limited to situations in which more direct measurements of either efficacy or toxicity are not available; examples include the monitoring of blood coagulation studies (rather than drug plasma levels) to control therapy with the anticoagulant drugs heparin and warfarin.

Given this well defined relationship of activity to serum drug concentration, therapeutic drug monitoring can provide invaluable information in a wide variety of clinical situations. Because many agents lack objective criteria to measure pharmacologic effect or predict toxicity, the use of serum drug level monitoring can help to establish therapeutic drug concentrations more rapidly to prevent periods of inadequate control or toxicity. This is especially true if the drug is to be administered prophylactically.

Compounds that demonstrate poor relationships between the dose administered and the resulting serum concentrations can best be monitored using serum drug concentrations. This situation may result from wide pharmacokinetic differences between patients. Agents with a narrow therapeutic index (i.e., small differences between therapeutic and toxic blood levels) or those for which the implications of a subtherapeutic response would be severe are often monitored to confirm a therapeutic serum level. Noncompliance may also be documented using laboratory analysis.

Sample Collection and Laboratory Analysis

The correct timing for collection of a sample in relation to the administration of a dose is essential, since the appropriate interpretation and application of the data are dependent on it. Ideally, the absorption and distribution phases should be complete and steady state should be reached before a sample is obtained. The correct timing in relation to the dose is therefore dependent on the product formulation, route of administration, and pharmacokinetic parameters of the drug (as discussed earlier). Timing is also dependent on the data desired (see table 3). Peak levels are obtained at a period estimated to result in maximum blood levels based on product formulation, route of administration, and absorptive characteristics. Trough levels are usually drawn just prior to administration of the next dose. Routine serum level monitoring done to document therapeutic levels is best done after steady state has been reached and should include a trough concentration if the drug has a short half-life. If a toxic or subtherapeutic response is clinically suspected, peak and trough levels should be supplemented with or replaced by "spot" levels at the time of the response. Documentation of noncompliance is usually done as a spot level, since most of these patients are ambulatory, thus making selection of an optimal sampling time impractical.

Table 3
Timing of Sample Collection for Drug Assay*

Desired Information	Time of Collection
Peak levels	Estimated point of maximum absorption
Trough levels	Prior to the next dose
Document drug toxicity	Peak level supplemented or replaced by spot level at the time of clinical toxicity
Document subtherapeutic response	Trough level supplemented or replaced by spot level at the time of subtherapeutic response
Therapeutic confirmation	Steady state trough levels may be supplemented by steady state peak levels if the drug has a short half life
Document noncompliance	Spot level

* Best accomplished following absorption and distribution phases after steady state has been reached

After the timing of the sample is determined and documented, it must be properly collected and stored for transportation to the clinical laboratory for analysis. The appropriate container must be selected to minimize interference with the assay and should be labeled with the appropriate patient data (name, room number, etc.). Also, the site of sampling is important. Collection from indwelling catheters containing heparin or those used for administering medication should be avoided. Selection of sites for venipuncture is dependent on the availability of venous access, but those done close to the site of drug administration may result in levels that are elevated because the drug has not been allowed to be diluted and distributed into the serum. The volume, type (serum or plasma) and storage of the collected sample depend on the type of assay to be utilized.

After the appropriate sample has been collected and transported to the laboratory, analysis using one of the variety of procedures may then be performed. Factors such

Table 4
Factors Affecting Serum Drug Concentrations and Their Interpretation

Drug characteristics	Patient characteristics
physiochemical properties	age
product formulation	sex
pharmacology/ pharmacokinetics	pregnancy
	genetic factors
Disease state(s)	organ function (hepatic, renal, etc.)
	body composition
Concomitant drug and food intake	Sampling and assay
	timing of sample
Drug therapy	sensitivity & specificity of assay
route of administration	
compliance	
duration of treatment	

as sensitivity and specificity of the assay must be considered, as well as the turn-around time to obtain results. The laboratory must also know what must be measured, since active metabolites may be measured depending on their concentration, degree of activity, and potential for accumulation.

Interpretation of Results

Interpretation of the results of serum drug level assays requires the integration of knowledge of a drug's pharmacokinetic profile and its influences with the clinical status and response of the patient. These data should first be correlated with the collection time of the sample in relation to the dose and duration of treatment to determine whether this value represents a peak, trough, or intermediate concentration and if a steady state has been reached. Many factors may influence drug serum concentrations and their interpretation, and must be considered before continuation or modification of drug therapy is done based on this information (see table 4).

The therapeutic range of a drug may be defined as a range of serum drug concentrations associated with high degree of efficacy and a low risk of dose-related toxicity.[7] Because this is based on data from the general population and could not be controlled for the variety of factors that may influence patient response, it is imperative that these data be correlated with clinical status to interpret the results. Patients may therefore respond to "subtherapeutic" levels or require "toxic" concentrations (based on this established therapeutic range) for adequate response.

Conclusion

The capabilities and applications of serum drug level monitoring are now beginning to be recognized. Because of the great impact of drug therapy on patient care, interest and knowledge regarding pharmacokinetics have skyrocketed, making individualized drug therapy a reality through integration of pharmacokinetics, clinical therapeutics, and analytical sciences. However, it is only with a general knowledge of basic principles of therapeutic drug monitoring that these capabilities can be applied and maximized. Therefore, the contribution of serum drug level monitoring is largely dependent on its appropriate use.

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SCIENTIFIC ARTICLE

Pulmonary Echinococcosis: The Geographic History Scores Again

Doris S. Kelsey, M.D. and Louis deS. Shaffner, M.D.

THIS is the story of a patient with a disease rarely seen in North Carolina. The patient was a 14-year-old white girl who was admitted to the North Carolina Baptist Hospital in Winston-Salem with a 4-week history of intermittent fever, fatigue, cough, and a five-pound weight loss. A roentgenogram of the chest obtained two weeks earlier revealed a well-defined lobulated density in the left lower lung field. Subsequently a one-week course of oral tetracycline and then five days of oral erythromycin resulted in no change in clinical or radiographic findings. The patient had been in Iran from 1976 to 1978 with her father who was on military assignment.

Oral temperature was 102° F, blood pressure 112/74, pulse 92 per minute, and respirations 20 per minute. There were no abnormalities detected on physical examination. The radiographic findings and environmental history suggested the possibility of echinococcus.

The hematocrit reading was 32 volumes percent, white blood count was 13,600 cells per cu ml with a differential count of 77 neutrophils, 14 lymphocytes, 7 monocytes, 1 eosinophil and 1 basophil. Total serum protein was 7.0 grams per decaliter with an albumin/globulin ratio of 3.1/3.9. Serum submitted to the Centers for Disease Control in Atlanta, Georgia for indirect hemagglutination to echinococcus revealed a titer of 1:512.

Radiologic procedures included sonic studies of the abdomen and computerized tomography of the head and revealed no additional cysts.

The preoperative diagnosis of hydatid cyst was confirmed at surgery. A basilar segmental resection of the left lower lobe with removal of the cystic mass was performed. Pathologic report revealed the presence of hooklets within the lesion. The cystic cavity was 4 cm in diameter with several smaller cystic lesions that did not communicate with the larger one. Bacterial culture of the surgical specimen grew non-typable *Hemophilus influenzae*. This secondary infection probably explained the febrile course.

Postoperatively, the patient received intravenous cephapirin sodium for three days and then oral cephalexin for a total of seven days. The patient was discharged on the seventh postoperative day and has remained symptom-free in the year since surgery.

Discussion

Echinococcosis (hydatid cyst) is a parasitic disease caused by infection with the larvae of *Echinococcus granulosa*, the dog tapeworm. The disease is endemic in many parts of the world with the greatest prevalence reported in Australia, South America, South Africa, the Soviet Union, and the Mediterranean. Most cases diagnosed in the United States are acquired in other countries although autochthonous cases have occurred.[1] Three cases of pulmonary echinococcosis in children from Arizona and New Mexico have been reported.[2]

Man is an inadvertent host of the disease usually infected by dogs that excrete the eggs in the feces. Dogs acquire the disease from ingestion of infected sheep or other intermediate hosts. Once the eggs are ingested by man, the larvae hatch in the intestine and are disseminated via hematogenous or lymphatic routes with production of hydatid cysts. The spread is via the duodenum into the portal system with the majority of cysts found in the right lobe of the liver.[3] In children, however, the lung is reported to be more frequently involved than the liver. The right lung is infected more often than the left; likewise, the lower lobes are more frequently involved than the upper ones.[4, 5] Although the majority of hydatid cysts occur in the liver or lungs, they may occur in any organ or in multiple sites. The cyst is estimated to grow about 1-2 cm per year. The latent period from infection to clinical symptomatology may be quite variable depending on the site of involvement. It may be especially prolonged in the liver where a large mass may not produce symptoms. At the extreme, an interval of 50 years from infection to clinical diagnosis has been reported.[3] The clinical symptoms associated with pulmonary hydatid cyst frequently include cough, hemoptysis, or chest pain. Some children may have pruritis. Roentgenographic evaluation, particularly ultrasound studies, is helpful in delineating the cystic nature of the lesion or multiple cysts. Long-standing lesions may be calcified. The most helpful laboratory test is the indirect hemagglutination test for echinococcus which is positive in about 85% of patients with liver cysts and 40% of patients with pulmonary echinococcosis. Eosinophilia is not typical.[1]

The differential diagnosis of lung cysts includes bronchogenic cysts, hamartomas, granulomatous lesions, and post-inflammatory tumors of the lung.

As in this case, a presumptive diagnosis of hydatid cyst can be made based on the environmental history, radiographic studies, and serologic findings. Definitive treatment is by surgical excision of the infected cyst or preliminary sterilization of the cyst contents with a scolicidal solution prior to evacuation by surgical aspiration.

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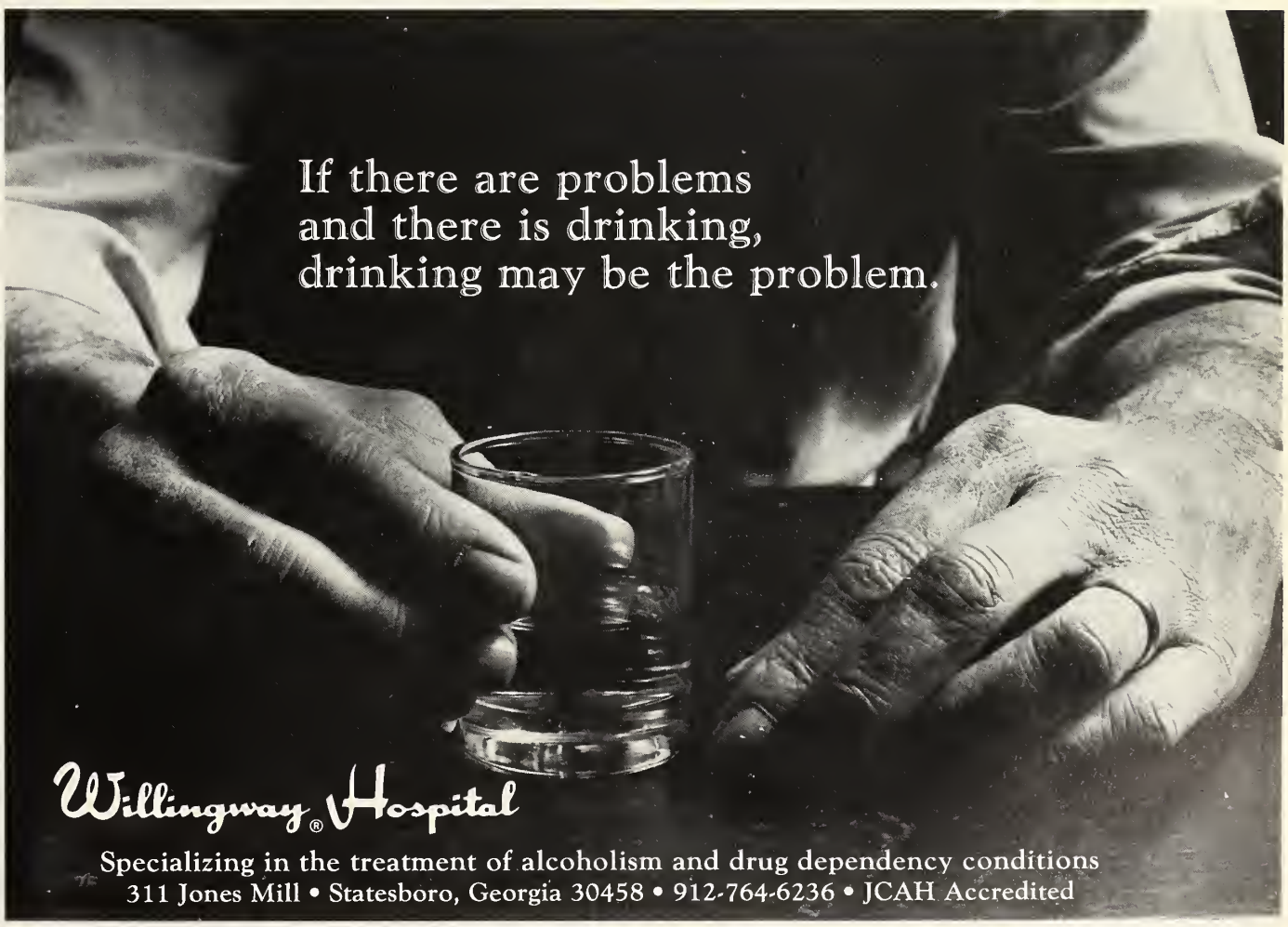
Cryosurgery has been successfully used in preventing rupture of the cyst during operation.[6] Special care must be taken to avoid spillage of the cyst contents during surgery, as this complication has been associated with anaphylactoid reactions and metastatic dissemination. Surgical techniques to reduce complications and recurrences have been described elsewhere.[4-6] Mebendazole[7] has been utilized for treatment of echinococcosis in patients with inoperable or advanced disease with encouraging results. Other investigational drugs in the treatment of this disease process include praziquantel[8] and albendazole.[9]

Acknowledgment

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SCIENTIFIC ARTICLE

The Role of the Argon Laser in Plastic Surgery

Ronald Riefkohl, M.D.

LASER is an acronym for *L*ight *A*mplification by *S*timulated *E*mission of *R*adiation. This radiation is non-ionizing and therefore non-carcinogenic.

The argon laser is an optical resonator filled with argon gas, and has a 100% reflective mirror at one end and a 95% reflective mirror at the opposite end. When a high voltage is applied across the resonator, the outer orbiting electrons of argon atoms are temporarily raised to higher energy levels. As the electrons drop back to the normal energy level, a photon of light of a specific wavelength and color is emitted. As this photon bounces back and forth between the two mirrors, it strikes another excited argon atom and stimulates the emission of a second photon of the identical wavelength and color. This process continues repeatedly, stimulating more excited atoms to emit photons cooperatively before they have time to do so spontaneously and independently. This amplification process results in a beam of intense, monochromatic, coherent, directional radiation, i.e., argon laser light, that is emitted through the partially reflective mirror and transmitted through fiberoptic cables to a handpiece used to aim the laser beam at the target tissue.[1]

Argon lasers produce visible blue/green light (488-514 nm) which is transmitted through clear aqueous tissues, but absorbed by pigments, particularly pigments of the complementary red color, such as hemoglobin. Cutaneous laser absorption by hemoglobin causes heat generation and coagulation of small vessels and adjacent tissue, resulting in vasocoagulation and a superficial second degree burn, which when healed will be a lighter color shade. Unfortunately, the argon lasers currently available penetrate skin to a depth of only 1.5 mm and will not coagulate vessels larger than 0.5 mm in diameter. Late histopathological skin changes are maximum at a depth of 0.1-0.4 mm, with compaction of dermal collagen, obliteration of a substantial number of dermal capillaries, and blunting of the rete ridges with epidermal atrophy as is seen after any cutaneous thermal injury.[2]

We have used a Cooper Medical Model 770, 5-watt argon laser (Cooper Medical, 88 Hamilton Ave., Stamford, Connecticut 06904) to treat 135 lesions. The beam was delivered through either a 1 mm or a 2 mm hand-held fiberoptic stylus. All patients with portwine stains first underwent a test spot treatment, during which a small area was treated to enable the patient to see the degree of improvement before submitting to extensive treatment as well as to eliminate any patient with a tendency to develop hypertrophic scarring. Treatment was not resumed for at least three months. Larger portwine stains were treated sectionally because of the substantial edema that occurs and to minimize potential difficulties with wound healing.

Patients with other vascular lesions or decorative tattoos ordinarily did not undergo a test spot treatment.

Treatment was done on an outpatient basis and under local anesthesia by infiltration of 1% xylocaine. For vascular lesions, the lowest power setting that will convert the red discoloration to a whitish-grey hue was selected. This is usually in the range of 0.8-1.2 watts, with an exposure time per area of 0.2 sec. For tattoos, the object is to achieve a deep dermal burn; therefore power settings of 2.6-3 watts with exposure time of 1-5 sec are necessary. After treatment, 1% silver sulfadiazine cream was applied to the burn wound until it healed. Treated vascular lesions ordinarily healed by 14 days, but most treated tattoos did not re-epithelialize for at least four weeks.

Table 1 summarizes the cutaneous lesions treated during the previous 18 months. Many of the patients with large portwine stains have not completed treatment and those patients treated during the past three months have received only a test spot.

The portwine stain is optimally treated with the argon laser, as no other treatment modality is as effective, particularly for larger lesions. Most portwine stains fortunately are in the papillary layer of the dermis, and are thus amenable to photocoagulation. The degree of color change is quite variable, but approximately 70% of patients will be benefited. Small superficial portwine stains located on the face are nearly 100% obliterated. The best results have occurred in patients with facial portwine stains that are dark red or light purple. Other favorable attributes include a superficial location, a fair complexion, and sluggish blanching and capillary refilling of the lesion. The results with portwine stains located on the trunk and extremities have been disappointing because of minimal color change and scarring. Telangiectatic vessels and spider nevi located

Table 1
Cutaneous Lesions Treated with Argon Laser

Lesion	Number
Portwine stain	76
Capillary-cavernous hemangioma	2
Decorative tattoo	22
Traumatic tattoo	2
Facial telangiectasia	21
Spider nevus	7
Post-rhinoplasty erythema	1
Acne rosacea	3
Angiokeratoma	1
Total	135

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on the face achieved nearly 100% obliteration.

Two small capillary-cavernous hemangiomas located on mucous membranes have diminished after treatment, but these lesions are expected to ultimately expand to their original size. No cutaneous capillary-cavernous hemangiomas have been treated.

Acne rosacea and post-rhinoplasty cutaneous erythema have both been treated successfully.

Superficial telangiectatic vessels located on the lower extremities have been photocoagulated unsuccessfully, in that initially there is complete obliteration, but after 8-10 weeks the vessels recanalize, probably because of their larger size.

Pigment removal from decorative tattoos has been approximately 95% complete; most patients had a few remaining speckles of pigment within a smooth atrophic scar. Traumatic tattoos have not responded to treatment, but experience has been limited to two patients.

The incidence of hypertrophic scarring with tattoos has been about 25%, and with facial portwine stains and other vascular lesions about 5%. Almost all the facial hypertrophic scars were located on the lips, chin, lateral nose, and nasolabial region. Several facial hypertrophic scars were successfully treated with repeated steroid injections. About 10% of the portwine stains on the extremities or trunk developed hypertrophic scars. There have been no other complications to date.

Recently, strawberry hemangiomas in infants have been treated with the purpose of precipitating involution but they are not obliterated by the laser itself.[3]

Patients under 12 years of age may have prolonged redness of the treated skin and are at a greater risk for hypertrophic scarring. Characteristically, portwine stains darken and thicken with aging and many also develop surface irregularities and "bubbling." Though significant lightening and smoothening will be anticipated in this age group, the color change is not as dramatic as in young adults.

Superficial capillary-cavernous hemangiomas confined to the skin may be benefited initially, but usually deeper components of the lesion may result in recanalization and recurrence. Since the argon laser will not penetrate intact skin, subcutaneous hemangiomas are not affected.

The other group of successfully treated cutaneous lesions includes facial telangiectatic vessels, spider nevi, acne rosacea, and post-rhinoplasty erythema. The vascular pathology in all of these lesions is superficially located and may be obliterated by laser photocoagulation. Due to the small size of the lesions and consequent minimal thermal damage, the risk of hypertrophic scarring is remote.

Decorative tattoos may be removed because there is non-specific absorption of argon light by metallic-oxide tattoo pigments. Rather than vasocoagulation though, the superficial skin is vaporized by the laser beam, so that the extent of thermal injury to the deep dermis is substantially greater than for a vascular lesion and the healing time is consequently prolonged. This accounts for the much higher incidence of hypertrophic scarring with commercial tattoos. Under the best conditions a depigmented and atrophic scar with a few speckles of tattoo pigment remains. These remaining tattoo speckles have been resistant to repeat laser treatment. Either the pigment in these areas is located at a deeper level of the skin, or it has become trapped within scar tissue during healing. Also, the silhouette of a tattoo will remain evident, so for obvious outlines such as letters, the surrounding skin should also be treated to disguise the nature of the original tattoo.

Curiously, traumatic tattoos have responded poorly, perhaps because of the associated scar tissue with the entrapped debris, or the foreign debris may be too deep in the skin.

Small vascular lesions or tattoos that are appropriately situated may be more easily managed by surgical excision, since the postoperative management is easier and the results are more predictable. Other situations that may preclude the application of the argon laser include patients with a dark complexion, since there is absorption of the beam by melanin and consequently less vasocoagulation and subsequent color change. There is also the theoretical risk that should significant obliteration of a vascular lesion occur, late skin depigmentation may be just as noticeable and distressing to the patient as the original vascular lesion.

Patients with a hypertrophic scar tendency probably should not be treated. Also, vascular lesions located on the trunk and lower extremity, particularly below the knees, are unlikely to change color sufficiently to justify the increased risk for hypertrophic scarring as well as the inconvenience and expense of the treatment.

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SCIENTIFIC ARTICLE

Gastric Bariatric Surgery at North Carolina Memorial Hospital: Factors Essential for Good Results

Charles A. Herbst, Jr., M.D. and Joseph A. Buckwalter, M.D.

IN 1975 a randomized clinical trial at North Carolina Memorial Hospital determined that gastric bypass (a gastric bariatric procedure) was as effective as and produced fewer complications than the jejuno-ileal bypass.[1, 2] On the basis of this experience we have in the last eight years used gastric bariatric operations in the treatment of morbid obesity. One of five operative procedures have been done on 575 patients.[3, 4] Patients receiving concomitant jejuno-ileal bypass takedown and those operated elsewhere who were referred because of complications are not included. Sex, age, ideal weight, real weight, and excess weight of all five groups were comparable.

Group 1, treated by gastric bypass Roux-en-y (GB-RY), was composed of 184 patients. Table 1 lists 58 complications in 41 GB-RY patients (22%). Splenic injury (6 patients) and anastomotic leak (6 patients) carried a high incidence of morbidity, usually associated with development of a subphrenic abscess (11 patients). The six patients who had staple separation were all in the group of 31 who received a single TA-90 cartridge application and led to our adoption of a double application or suture-reinforced staple line. There were nine patients who had stomal obstruction. Four responded well to medical management and did not require surgery. Five required revisional surgery. Two patients developed marginal ulcers. One required surgery to excise the ulcer and reduce the size of the pouch which was too large. The other patient responded well to cimetidine and has had no trouble since. There was one surgically related death.

Group 2 was composed of 69 patients who had a gastric bypass loop gastroenterostomy (GB-loop). This procedure also produced a high incidence of technical complications including splenectomy (2 patients), anastomotic leak (2 patients), abscess (4 patients), and staple line separation (2 patients). There was one surgically related death.

In groups 1 and 2 the pouch, although not measured, was estimated to be between 50 and 60 ml. The stoma was 1.0-1.2 cm in diameter by measurement over a calibrated tube. The stomach was transected in the first 12 GB-RY patients and 9 GB-loop patients. Following Alden's report in 1977, describing the use of stapling instruments,[5] we adopted a single application of the TA-90 stapler to partition the stomach in 31 GB-RY patients. Later, a double application of the TA-90 or a single TA-90 application reinforced with a nonabsorbable suture was used.

Group 3 contained 40 patients who had a greater curvature gastroplasty (GP). In these patients, the stoma was created by removing staples at the greater curvature end of the TA-90 stapling instrument. In eight patients, no staples were removed, but a C-clamp was used as described by Gomez.[6] A double application of the TA-90 was used and the pouch was estimated to be between 40 and 50 ml. The stoma was reinforced with an inverting running Lembert nonabsorbable suture over a 10 mm bougie.

A major problem was stomal obstruction in 7 patients (table 1). For this reason we abandoned greater curvature gastroplasty. Four patients had functional obstruction in the presence of an adequate stoma demonstrable by barium and endoscopic studies. The factors responsible for stomal obstruction include edema, reduced blood supply, and crushing the area between the jaws of the stapling instrument. There were no deaths in this group.

Group 4 contained 223 patients who had a gastrogastrostomy (GG) anterior to a double-applied TA-90 staple line. Originally, the pouch was 40-50 ml but later it was made 20-25 ml by a less transverse and more oblique placement of the staples. This change allowed substitution of the TA-55 for the TA-90. The stoma, originally 1.0 cm in diameter, was also made 0.8 cm in diameter enclosed circumferentially with an absorbable running inner layer. Staples made the outer posterior layer, and a nonabsorbable running Lembert suture made the anterior outer layer. This procedure caused fewer technical complications and those that occurred were less serious than in groups 1, 2, and 3. Eleven patients developed phytobezoars requiring endoscopic removal or enzymatic digestion. Having a bezoar in fact proved to be a valuable learning experience since no patient developed a second bezoar. There was one surgically related death.

Group 5 was composed of 49 patients having a vertical banded gastroplasty (VBG). Three patients (6%) experienced surgically related complications (table 1). A window is made through both walls of the stomach just above the crow's foot and along the lesser curvature. A double application of the TA-55 staple up to the angle of His through this window creates a 20-25 ml pouch. A 1.5 x 7.0 cm polypropylene mesh collar is sutured to itself around the

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TABLE 1
Complications in 575 Morbid Obesity Operations

	GB-RY	GB-Loop	GP	GG	VBG
Splenectomy	6	2	0	0	0
Leak	6	2	1	3	1
Abscess	11	4	0	2	0
Staple separation	6	2	1	2	0
Obstruction	9	0	7	5	0
Bezoar	0	1	1	11	0
Afferent loop	0	2	0	0	0
Reflux	0	2	0	0	0
Marginal ulcer	2	0	0	0	0
Death	1	1	0	1	0
Miscellaneous	17	15	2	23	3
Percent patients	22%	32%	28%	19%	8%

stoma to provide an outlet circumference between 5.0 and 5.5 cm.

There was good weight reduction in groups 1, 2, and 3 but the morbidity was high (table 2). The weight loss was less satisfactory in group 4 but complications were less frequent. In group 5 the weight loss appears promising and the complications are reduced. A longer followup is needed for group 5 before we can adopt vertical banded gastroplasty as the operation of choice.

Our Learning Curve

From group 1, the Roux-en-y gastrojejunostomy, we learned the importance of correctly sizing the proximal pouch and stoma. If either of these is too large, the results are not optimal.

In groups 1, 2, and 3, the greater curvature of the stomach is mobilized leading to a high incidence of splenic injury, splenectomy, and subphrenic abscess. Because the greater curvature is devascularized, there is a tendency for ischemia, leaks, edema, and obstruction.

The gastrogastrostomy partition performed in group 4 allowed us to avoid mobilizing much of the greater curvature and short gastric vessels, thereby reducing the incidence of splenectomy, abscesses and leaks. Long-term weight loss results are not good because of pouch and stoma structure.

The vertical banded gastroplasty avoids most of the technical problems created by the procedures done on patients in groups 1 through 4. The pouch is small at 20-25 ml compared with the 50-60 ml size in the early operations. The partition is secured with a double application of TA-55 staples. Previous experience of one application in 31 patients in group 1 showed a 20% failure of the partition. The stoma in the vertical banded gastroplasty is reinforced with a polypropylene mesh to prevent strictures. Earlier procedures used a nonreinforced stoma or a suture-reinforced stoma which frequently would dilate. This is especially true in the patients who had a gastrogastrostomy. In addition, the vertical banded gastroplasty has other technical advantages compared with previous operations. The short gastric vessels are not divided and therefore injury to the spleen is avoided. Although theoretically the wound is contaminated by creation of the gastric window, there is no open anastomosis to provide gross contamination for contributions to abscess formation. The only information lacking on vertical banded gastroplasty is whether or not the patients will have a weight loss comparable to the other operations. Preliminary data from our institution are encouraging. Using a 5.0 cm band, Mason et al. have reported 58% excess weight loss and Doherty has shown a 68% excess weight loss at one year.[7]

Table 2
Percent Excess Weight Loss Following Five Gastric Operations

Time since operation	GB-RY	GB-Loop	GP	GG	VBG
6 months	41	39	45	40	41
1 year	57	59	65	48	—
2 years	57	62	65	39	—

The first 3 groups of patients (GB-RY, GB-Loop, GP) have been followed from one to five years. Those treated with GG have been followed as long as three years. VBG patients have been followed less than one year.

Patient selection is as important as the type of surgery. Success is dependent on a well-motivated and cooperative patient. Experience is the major teacher that guides the surgeon to select patients who are cooperative and compliant.

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SCIENTIFIC ARTICLE

A "New" Cause of Diarrhea?

Richard A. Davidson, M.D.

FOR the next topic in our series about parasitic infections in North Carolina, I have chosen to discuss an infection that we have not yet documented at North Carolina Memorial Hospital. The reason for this choice is that Cryptosporidiosis is something you will be hearing a great deal more about in the next few years.

Cryptosporidium is a small (4-6 micrometers) protozoan parasite which has been known in veterinary circles for some time as a causative agent of diarrhea in calves, lambs, goats, and poultry. It is in the same suborder as Toxoplasma. Unlike most parasites, Cryptosporidia are not species-specific; organisms recovered from one host have been easily transmitted to other species. The implications of this fact are responsible for the recent interest in the organism.

The life cycle includes both sexual and asexual stages; the organisms attach to enterocytes and undergo maturation. The length of the life cycle seems to be associated with the host's age and immunologic competence; in 1-day old lambs the life cycle may be as short as 72 hours.[1] The size of the organism makes its recovery in stools very difficult unless concentration techniques are carried out. The diagnosis has been made most frequently by biopsy, which shows dot-like organisms imbedded in the brush border of the enterocytes on standard stains.

The first case of human Cryptosporidiosis was reported in 1976.[2] The overwhelming majority of subsequent case reports consisted of patients who were immunocompromised, most frequently from immunotherapy or congenital immune deficiency syndromes; more recently it has been found in the acquired immunodeficiency syndrome and in patients in high risk categories for AIDS, such as homosexuals, hemophiliacs and Haitians. In some immunocompromised individuals the infection was fatal, with severe uncontrollable diarrhea, dehydration, and electrolyte abnormalities.

In 1982 Cryptosporidia enteritis was reported in a professional baseball player in otherwise excellent health.[3] The patient had worked as a horse trainer just prior to the onset of his illness, which was a severe dysentery lasting one month before gradually improving without therapy. Shortly after this report an outbreak of Cryptosporidia occurred in 12 immunocompetent individuals who had direct contact with infected calves during outbreaks of calf Cryptosporidiosis.[4] The infection was transmitted experimentally to calves and mice from humans.

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Two large scale screening studies found a high prevalence of Cryptosporidia in stools of patients with gastroenteritis. Tzipori et al,[5] in Australia, found Cryptosporidia in the stools of 4.1% of 884 hospitalized patients with gastroenteritis; none of 320 patients without gastroenteritis was excreting the organisms. Jokipii et al[6] studied stools sent by general practitioners in Finland. Of 154 stools examined for Cryptosporidia, 14 (9%) were positive. The authors compared the clinical syndrome with giardiasis and found the incubation periods to be similar (median 7 days); the course of the illness was shorter (10 vs. 25 days) and more abdominal pain and cramping were seen in the patients with Cryptosporidiosis. Giardiasis caused more bloating, anorexia, and weakness.

Cryptosporidiosis seems to be largely self-limited in healthy adults, with resolution of the illness within 10 days in half of reported cases. It has been estimated that up to 40% of acute diarrheal illness may be caused by cryptosporidia, especially in more rural areas such as North Carolina. A three-step stool examination, which is more sensitive than biopsy, has recently been described.[7]

Over forty antimicrobials have been tested against the organism without evidence of efficacy. Currently the only therapies that hold promise are spiramycin, a drug similar to erythromycin and clindamycin, and the combination of quinine and clindamycin.[8] Both regimens were given to AIDS patients with some response, although most patients did not respond to either. Continuing study by medical and veterinary institutions may lead to the development of effective therapy. Knowledge of the mode of transmission of the organism may alert physicians to outbreaks of this infection in persons exposed to farm animals and other persons at risk, and may prevent extended work-ups and inappropriate use of medication.

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SCIENTIFIC ARTICLE

Caffeine — A Drug with Multiple Points of Entry

Gregory C. Khoury, M.D. and Allan A. Maltbie, M.D.

MY interest in caffeine-related problems was aroused by a 42-year-old white nurse who had a seven-year history of psychiatric difficulties. Past diagnoses included anxiety neurosis, hysterical personality, hysteroid dysphoria, and panic attacks. The patient complained of chronic insomnia, symptoms of anxiety, and irritability. She reported spells of palpitations, at times associated with facial flushing and headache with a worsening of symptomatology through the day. Her scholastic and work performance had deteriorated over the preceding seven years. A detailed history revealed that over this interval the patient had been drinking in excess of 12 cups of brewed coffee per day and additionally one gallon of diet cola. For persistent insomnia, she had used a nightly dose of from 15-20 mg of Valium with a partial sleep response. Benadryl and Elavil had been administered without improvement. Over the seven years the diagnosis of caffeinism had not been entertained despite multiple consultations with several physicians. The patient accepted my treatment recommendations to begin short-term psychotherapy and a gradual taper of caffeine intake. Her symptoms dramatically improved with cessation of headaches, palpitations, and symptoms of facial flushing. She became less irritable and was able to sleep. Concentration and work performance improved.

The patient was clinically observed to maintain this symptomatic improvement for a three-week period, during which psychotherapy continued. She then left psychotherapy due to emerging fears of closeness and anger over the upcoming termination. This occurred, however, well after the superimposed caffeinism was diagnosed and treated to full resolution.

The proper treatment of caffeinism is a gradual taper of caffeine with conservative management of any withdrawal symptoms.[1] Withdrawal headaches are best managed with plain aspirin or acetaminophen since caffeine may be an additive in some of the combination agents. The sluggishness and dysphoria of withdrawal generally respond to reassurance and typically abate once the withdrawal process is complete. During the withdrawal taper, ingestion of caffeine after 5:00 p.m. should not be allowed in an effort to prevent insomnia. The complaint of insomnia generally abates quickly with the cessation of evening caffeine, and sedative hypnotics are generally not needed in this clinical situation.

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Caffeinism

Caffeinism may be defined as a pathological dependence on caffeine. Here a large volume of caffeine is consumed and associated with symptoms of diuresis, insomnia, hyperirritability, anxiety, weight loss, bouts of flushing and chilliness, headache, palpitations, tachycardia, and mild increase in body temperature. Related psychiatric symptoms include anxiety, depression, psychophysiologic reactions, and even psychosis.[1, 2] Withdrawal symptoms, which usually include fatigue, sense of dysphoria with headache, and mild confusion with decreased reaction time have been reported. These symptoms of withdrawal are reversed by the administration of caffeine. The degree of severity of symptoms with caffeinism seems directly proportional to the size of the ingested dose of caffeine.

Sources, Dose and Stimulant Effects

Caffeine is ubiquitously available today in a variety of socially acceptable beverages and over-the-counter preparations including coffee, tea, cola drinks, hot cocoa, analgesics, dietary aids, diuretics, and stimulants.

Popular misconceptions exist as to the content of caffeine in many beverages. The most prominent of these is the notion that brewed coffee is twice as caffeine-rich as tea and three times as caffeine-rich as cola drinks.[3] In reality, the 2% caffeine content of tea leaves is often higher than that of coffee beans, which ranges from .7% to 2%. Furthermore, once prepared the beverages contain about equal amounts of the alkaloid (100-150 mg per 8 oz cup). Instant coffee contains 86-99 mg/cup and a cola drink contains 25-35 mg/cup or 35-55 mg/12 oz bottle. Substantial inconsistencies occur in the literature as to the amount of caffeine to be found in a cup of brewed coffee. These inconsistencies serve to confuse the correlation between symptom cluster and ingested dose and may contribute to substantial underestimation of the amount of caffeine ingested by individuals.

Caffeine ingestion may cause temporary exacerbation of endogenous anxiety disorders as well as psychotic thought disorders. Freitas and Schwartz[4] noted the negative effects of caffeine in chronic psychiatric inpatients and published evidence of significant improvement in patient management with reduction of symptoms where caffeine utilization was reduced. After one week of substitution of decaffeinated coffee for regular coffee, patients with manic depressive disorder, organic brain syndrome, and schizophrenia demonstrated significant decrease in hostility, suspiciousness, anxiety levels, and irritability. Return to

regular coffee reversed this improvement and resulted in significant increase in anxiety, somatic concerns, irritability, hostility, and manifest psychotic symptomatology.

Gilliland and Andress[5] reported a statistically higher incidence of anxiety and depression in moderate and high caffeine consumer groups compared with abstainers. The high consumer group also reported higher levels of symptoms of caffeinism, higher frequency of psychophysiologic disorders and lower academic performance when compared with abstainers.

Greden et al.[6] reported a statistically significant increase in anxiety and depression symptomatology in high caffeine consumers (750 mg or more) compared with moderate and low consumers. In addition, high consumers reported more problems with physical health and greater use of sedative hypnotics and tranquilizers than did moderate and low consumers.

Victor, Lubestsky, and Greden[1] compared reported somatic symptoms among low, moderate, and high caffeine consumers. Diuresis, insomnia, headache, diarrhea, anxiety, tachycardia, and tremulousness were most commonly reported in descending order of frequency in the study. Differences were common among high, moderate, and low consumers, and dose response associations seemed apparent. This study seemed to confirm the hypothesis of the dose response death.[6] Although the lethal dose of caffeine is estimated at 10 grams,[6] a review of all reported cases reveals fatalities resulting from ingestion of 3 to 50 gm of caffeine. In these fatalities, sources of caffeine included over-the-counter diet aids, concentrated caffeine tablets, triacqua tablets, and erroneous administration of caffeine in sodium benzoate solution by hospital personnel.

A Word to the Wise

Drug histories are notoriously difficult to take. Drugs creep in from every nook and cranny — even in drink and food. Remember caffeine when you are looking for symptoms that may be due to drugs.

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Antitrust and Physician Payment

Michael R. Pollard

THE purpose of this paper is to review antitrust principles and laws as they relate to physician payment. On their face, the antitrust statutes are deceptively simple. Unlike many federal statutes, the antitrust statutes are very brief and written in a relatively straightforward style. However, the body of antitrust law is largely the result of judicial interpretations of those statutes, and the opinions in antitrust cases can be long and complicated expositions of fact, law and economics. Antitrust cases typically raise many factual questions and the resolution of those questions often turns on sophisticated economic analysis of the competitive effects of the business practices under review by the court. Because this paper is intended for a well-informed but essentially nonlawyer audience, it is not heavily footnoted and most statements are not qualified by numerous *caveats* as they would be were it written for antitrust attorneys or economists. My intent here is to inform and guide the interested reader through an area of the law that is increasingly relevant to the issue of physician payment.

I. The Origins and Elements of Antitrust Analysis

A. Historical Underpinnings

Every society must order its economic activity according to a basic framework. Despite a heavy overlay of government regulation, the United States economy is based on the price system and competition. The price system conveys information to both producers and consumers and it creates incentives to produce goods and services efficiently. It also stimulates producers to innovate and offer new services that generate as well as respond to consumers' preferences. In competitive markets, producers will deliver goods and services that the majority of consumers demand. Competitive markets operate on the basis of consent and do not force individuals to act against self-interest.[1] The federal antitrust statutes were enacted to ensure that market competition is not unreasonably restrained by certain private agreements or practices. These statutes attempt to promote vigorous competition among many sellers: they are based on the premise that such a system will foster economic efficiencies. They were not designed to redistribute income or to achieve other social policy goals.

Contemporary antitrust and trade regulation laws find their antecedents in English Common Law.[2] During the thirteenth century in England, when commerce was primarily confined to local markets, the following activities were indictable offenses: 1) buying goods before they came to market; 2) buying goods in large quantities and selling them in smaller amounts; 3) buying crops before they were harvested. These were the so-called "middleman offenses": they were grounded in the belief that middlemen raised prices without achieving any useful business or social purpose.

English towns during the fifteenth and sixteenth centuries typically restricted trading by strangers through granting monopolies to local business interests, such as the trade guilds. The English Crown also engaged in granting monopolies as a means of raising revenue. Restraints on trade became so ubiquitous and burdensome that Parliament in 1623 enacted the Statute of Monopolies which invalidated all monopolies with exceptions for patents on new inventions, some monopolies granted by towns and guilds to establish more orderly trade relationships, and Parliamentary grants.[3]

English Common Law conspiracy doctrines influenced the prohibitions against unlawful conspiracies found in current antitrust statutes. These doctrines condemned otherwise lawful acts if they were committed by several individuals with the intent to achieve an "unlawful" purpose. Unlawful in this context meant "contrary to public policy."

The seeds for the antitrust statutes in the United States were sown during the rapid economic growth of the second half of the nineteenth century. This period spawned tremendous changes in industrial production and transportation, but it was marred by periodic and severe economic depressions. Populism, which arose out of discontent among agricultural and small town interests, gained many supporters and generated pressure for fundamental monetary and business reforms. The incidence of financial scandal and public corruption was high during this period, and many examples involved large trusts and monopolies such as the railroads and the oil companies. Certain markets were controlled by monopolists, but even in those markets where competition did exist, predatory pricing and other unfair business practices were commonplace.

B. The Antitrust Statutes

Despite the scandals and corruption of the late nineteenth century, public sentiment did not favor government takeover of basic industries or even stringent government regulation as the remedy for marketplace abuses. Instead, Congress trusted competition to police the market and free it of abusive private restraints. Accordingly, Congress enacted the Sherman Antitrust Act in 1890 which condemned monopolies and contracts, combinations, and conspiracies that restrain trade.[4]

From the Office of Policy Analysis, Pharmaceutical Manufacturers Association, 1100 Fifteenth Street, NW, Washington, DC 20005. The views expressed here are the author's and do not necessarily reflect the views of the Pharmaceutical Manufacturers Association or any of its member companies.

During the next two decades, the courts relied on the Sherman Act to strike down price fixing by railroads, the merger of two large western railroads, and three large trusts that controlled the meat, oil, and tobacco industries. Violations of Sections 1 and 2 of the Sherman Act are criminal offenses and can be punished by up to one year imprisonment and fines. The Act is enforced by the Justice Department.

In 1914, Congress supplemented the Sherman Act by enacting the Federal Trade Commission Act (FTC Act)[5] and the Clayton Antitrust Act.[6] The FTC Act appears to have emerged from both business concerns about the lack of an administrative commission or agency under the Sherman Act to provide guidance on which trade practices were lawful or unlawful, and those who believed business practices needed to be policed by a strong, independent commission with investigative and law enforcement powers. Members of this latter group felt that the Sherman Act was too general in its scope to provide adequate protection from unfair trade practices and that the Attorney General was not sufficiently insulated from political pressure to vigorously enforce a statute that often ran counter to strong business interests.[7]

The Federal Trade Commission Act prohibits "unfair methods of competition" and "unfair or deceptive acts or practices" affecting interstate commerce. Under judicial supervision and congressional oversight, the FTC is free to work out the exact meaning of unfairness or deception in the context of particular cases. In addition, as the result of amendments to the FTC Act in 1975, the Commission is authorized to promulgate trade regulation rules delineating and prohibiting unfair acts or practices on an industrywide basis. This rulemaking authority has embroiled the FTC in several heated controversies with industry groups. The FTC issues cease and desist orders and can impose civil penalties or require consumer redress in certain cases.

The Clayton Antitrust Act was enacted to provide legal remedies for certain practices that were not specifically covered by the Sherman Act. It prohibits 1) price discrimination; 2) sales on the condition that the buyer must stop dealing with the seller's competitors; 3) certain corporate mergers; 4) interlocking corporate directorates; and 5) certain common carrier transactions. The Clayton Act is enforced by both the Justice Department and the Federal Trade Commission, and violations of the Act are civil in nature.

C. Elements of Analysis

The antitrust laws are aimed at "unreasonable" restraints on trade and competition, even though a literal reading of Section 1 of the Sherman Act might imply that *all* contracts and agreements that restrain trade are prohibited. In the 1911 case of *Standard Oil Company* v. *United States*,[8] Chief Justice White first articulated the standard of reasonableness, or "rule of reason," that guides the courts in reviewing the legality of particular trade restraints. The elements of the "rule of reason" test were further elaborated in the case of *Board of Trade of Chicago* v. *United States*.[9] Here, the Supreme Court held that the true test of legality for a restraint of trade is whether it merely regulates and promotes competition, or whether it suppresses or destroys competition. In order to make this determination, courts must review the nature of the business in question, its condition before and after the restraint was imposed, the history of the restraint, and the purposes or ends for which it was adopted.

The "rule of reason," adopted by the Supreme Court more than 70 years ago, is the principle that still guides judges today in antitrust cases. However, it is a somewhat vague standard and it leads to extensive factual analysis, including costly economic studies. Thus, the courts have decided to dispense with a full-blown rule of reason analysis in certain cases involving restraints so blatantly anticompetitive that they are deemed to be *per se* unreasonable and illegal.[10] The courts have held the following activities to be *per se* violations of the antitrust laws: price fixing, division of markets, group boycotts, and tying arrangements.

D. Application of the Antitrust Laws to the Professions

Prior to 1975, the antitrust laws were of little concern to the professions. But, in that year, the Supreme Court struck down a minimum fee schedule imposed by a bar association in the case of *Goldfarb* v. *Virginia State Bar*.[11] The case is significant because the Court rejected the argument that the learned professions were exempt from the antitrust laws and did not engage in "trade" or "commerce" as those terms are used in the antitrust statutes. The Court concluded that Congress did not intend for professionals to be exempt from antitrust scrutiny.[12]

Three years later, the Court ruled on an ethical prohibition on competitive bidding imposed by the National Society of Professional Engineers and reiterated that the professions must comply with the antitrust laws.[13] The Court emphasized that the primary objective of antitrust is to promote competition and that courts, in reviewing antitrust cases, are limited to making judgments about the competitive impact and economic significance of the challenged restraint. The Court rejected the argument that judges should decide whether competition in a particular context is socially good or bad: the justices said that such questions should be decided by Congress.[14] However, the Court did acknowledge that the professions may merit special antitrust consideration because they do differ from other business services.

These decisions laid the groundwork for numerous investigations of restraints on professional practice by antitrust enforcement agencies, both at the federal and state levels. The Department of Justice has investigated architects, accountants, civil engineers, mechanical engineers, and physicians' specialty societies. The Federal Trade Commission has reviewed restraints imposed by lawyers, accountants, real estate brokers, physicians, dentists and veterinarians. States like Ohio, West Virginia, and Arizona have focused their investigations primarily on health professionals.

The most important law enforcement action brought by the Federal Trade Commission against a professional organization was the *American Medical Association* case.[15] Here, the Commission found that the AMA had prohibited almost all forms of truthful advertising and solicitation

through enforcement of various provisions of its code of professional ethics. Although the Commission found the AMA's restrictions on truthful advertising to be illegal, its opinion in the case states that the " . . . AMA has a valuable and unique role to play with respect to deceptive advertising and oppressive forms of solicitation by physicians." The Commission's order expressly provides that the AMA may adopt and enforce rules to prohibit such practices.

The FTC's *AMA* case was also a challenge to the AMA's so-called "contract practice" rules. Under those rules, it was unethical for a physician to sign a contract with a "lay" hospital, or HMO, if there was "underbidding" for the contract, or if the compensation was "inadequate" based on the fees usually charged in the community. These restrictions were, in some respects, quite similar to the rules against competitive bidding that the Supreme Court found illegal in the *Professional Engineers* case. The Commission ordered the AMA to eliminate these restrictions, which they did in their revised Principles of Medical Ethics.

II. Effect of Antitrust on Professional Practice

The fact that the antitrust laws are fully applicable to health professionals does not mean that they cannot engage in self-regulation or that restraints on their conduct will be treated in exactly the same way as a similar restraint on the conduct of a group of businessmen. Certification by medical specialty groups is an example of self-regulation that is reasonable provided the certification criteria and procedures are fair and the certification decisions are made objectively, on the basis of competence. Ethical rules that have the purpose and effect of prohibiting false or deceptive advertising are another example of permissible, in fact highly desirable, self-regulation. Insofar as health and other professional services markets are truly unique, traditional antitrust analysis is sufficiently flexible to take such conditions into account in considering whether a particular practice has had an unreasonably anticompetitive effect.

It is also clear that the antitrust laws do not interfere with state regulation of the professions. In *Bates* v. *Arizona State Bar,*[16] the Supreme Court rejected an antitrust challenge to restrictions that the Arizona Supreme Court had imposed on attorney advertising. The Court did this because the antitrust laws proscribe certain private actions but do not extend to anticompetitive practices that are sanctioned by the states. The Court has said on numerous occasions that immunity from the antitrust laws is warranted when the anticompetitive activity is conducted pursuant to a clearly articulated and affirmatively expressed state policy that is actively supervised by the state itself: this is the so-called "state action" doctrine.[17]

Despite the above mentioned limits on the scope of antitrust scrutiny, whenever professionals seek to influence fees or payment, antitrust concerns will be raised. Following *Goldfarb's* condemnation of minimum fee schedules as price-fixing, two elements of how fees are structured in medical markets became targets for antitrust scrutiny by law enforcement officials — i.e., relative value studies[18] and medical society control of Blue Shield plans.[19]

Relative value studies attach a series of numerical weights to medical procedures. The weights indicate the proportional value of each procedure to all others included in the study. Such tables are not fee schedules, but they can be easily converted to them by multiplying each proportional value by a dollar conversion factor. The Justice Department and the Federal Trade Commission saw the relationship between relative value studies and the illegal pricing formulas used by other industries to set prices, and enjoined them or obtained consent decrees governing their future development and use. More recently, however, a federal district court rejected the argument that a relative value study was a form of price-fixing that constitutes a *per se* violation of the Sherman Act.[20] It is not clear how the case would have been resolved had the Justice Department introduced evidence on the adverse economic effects of the scheme and the court had based its decision on a rule of reason analysis.

Medical society control of Blue Shield was, at one time, a target for antitrust enforcement agencies. During the late 1970s, it looked like the Federal Trade Commission might initiate a rulemaking proceeding challenging the medical profession's influence over the policies and practices of Blue Shield plans. This initiative ultimately was abandoned by the FTC, but not before other medically dominated organizations had taken some steps toward including more nonmedical representation on their governing boards.

In the area of physicians' fees and payment arrangements, the antitrust laws clearly prohibit economic boycotts, both maximum and minimum price fixing, and attempts to monopolize the provision of services in a market. The antitrust laws do *not* prohibit professional consultation with health insurers, peer review of professional practices or utilization of hospital facilities, disciplinary actions by professional societies, or the formation and participation in prepaid health care plans where the physicians are sufficiently integrated into the financial structure that they would share in the risk of loss should the plan fail to meet its commitments. The legality of relative value studies, professional participation in peer review of fees, exclusive contract arrangements with hospitals or other institutional providers, and participation in less than fully integrated health care plans is unclear at this time.

III. The Effect of the Antitrust Laws on Insurers

The McCarran-Ferguson Act exempts from the antitrust laws the "business of insurance" to the extent that it is regulated by state law and does not involve acts of "boycott, coercion, or intimidation."[21] In a series of cases, the Supreme Court has explained and progressively narrowed the scope of this exemption. In *St. Paul Fire & Marine Insurance Company* v. *Barry,*[22] the Court stated that the term "boycott" included concerted refusals to deal with consumers, as well as competitors, within an industry. In *Group Life & Health Insurance Company* v. *Royal Drug Company,*[23] the Court set out three criteria for deciding whether a practice falls within the business of insurance: 1) the practice must transfer or spread a policyholder's risk; 2) the practice must be an integral part of the policy relationship between the insurer and the insured; and 3) the practice must be limited to entities within the insurance industry. In 1982, the Supreme Court held that the McCar-

ran-Ferguson Act does not remove peer review of professional fees from the purview of the antitrust laws.[24] This does not mean that peer review is illegal, but merely that it is not exempt from antitrust scrutiny.

The McCarran-Ferguson Act exemption has been asserted by professionals in the context of antitrust cases when their activities were related to health care financing considerations and, arguably, were part of the business of insurance. While considerable ambiguity continues to exist concerning the scope of this exemption, the Supreme Court's decisions make it clear that it, like all exemptions from the antitrust laws, will be narrowly construed.

For several years, the commercial health insurance companies have asserted that they are unable to compete effectively with Blue Cross/Blue Shield plans in most markets because their market shares are too small for them to bargain aggressively with hospitals or other providers. In order to attain more leverage in these markets, they suggest that they should be able to share data among themselves on costs and utilization but claim that they are precluded from doing so because of the antitrust laws. The insurers never clearly stated just what types of information they wanted to pool and share with their competitors, and they never officially requested either the Justice Department or the Federal Trade Commission to review the matter and provide either informal or formal advice on the legality of such arrangements. In November 1983, Senator Arlen Specter introduced a bill entitled the "Health Care Cost Containment Act of 1983" which, if enacted, would grant antitrust immunity to insurers who collaboratively collect data on health care costs and jointly negotiate prices with hospitals, physicians and other health care providers.[25]

IV. New Methods for Paying Physicians

Antitrust has long been a tool that proponents of alternative delivery systems have used to ease their entry into traditional health care markets. When traditional fee-for-service physicians have threatened to boycott HMOs or the physicians who affiliate with them, the antitrust laws have been an effective means for stopping such anticompetitive practices from coming to fruition. Similarly, efforts by organized medical groups to discourage price competition or prohibit the disclosure of fees have been successfully challenged under the antitrust statutes. Today, the pressure to curb rising health care costs is forcing even traditional physicians to consider participating in a variety of new organizations that promise to be more cost conscious than older methods for paying physicians but that also preserve most of the characteristics of fee-for-service practice.

The growth and development of these organizations has been concentrated primarily in California and other western states.[26] The term "preferred provider organization," or PPO, was coined by InterStudy to describe many of these new physician groups. Although PPOs can be sponsored by underwriters, providers, employers, or others, they seem to share four basic characteristics: 1) insurers or other third party payers contract with a panel of providers to furnish services; 2) a negotiated fee schedule (normally discounted from what the provider usually charges) and a promise to pay the providers promptly; 3) some form of utilization review; and 4) patients are not limited to the PPO panel but instead are encouraged to use the panel members through incentives such as reduced deductibles or no copayments. PPOs appear to have the potential for creating competition in both the financing and the provision of health care by offering price and coverage options that increase the economic incentives to control fees and utilization levels.

Structuring the fee schedule or discount may pose problems for some PPOs given the Supreme Court's decision in *Arizona* v. *Maricopa County Medical Society*.[27] Here, the Court held that it was *per se* unlawful for physician members of a foundation for medical care to agree jointly on the maximum fees that could be claimed in payment for services rendered to policyholders of foundation-approved insurance plans. For a variety of reasons, the *Maricopa* case has left the law in this area uncertain.

The decision is clear that the peer review and administrative functions performed by the medical care foundations did not prevent application of the *per se* rule; it also clarifies that competitors who have achieved sufficient operational integration by forming some sort of partnership or joint venture can jointly set prices without *per se* condemnation. But, by failing to supply us with an analytic framework, the Court missed an important opportunity to clarify a complex and critical aspect of price fixing law. *Maricopa* does not make it easier to discern when competitors acting in a joint enterprise have sufficiently integrated their operations so that an agreement they reach on price would be analyzed by the courts under the rule of reason as a joint productive arrangement, rather than being automatically condemned as naked price fixing. The Court gave no useful guidance for physician groups that may be willing to integrate more than was evident in *Maricopa,* but who might not wish to go as far as establishing partnerships or other joint ownership arrangements. This uncertainty may discourage the formation of alternative delivery systems with the potential for enhancing price competition and efficiency.

While the Supreme Court's decision in *Maricopa* certainly does not tell us much about what physicians can do in relation to prepayment plans, it surely does not mean that physicians who have achieved significant integration can never control payment decisions in a prepayment plan. Despite *Maricopa,* there are some observations I can make about provider groups and PPOs:

—A group of providers could combine their practices into a single group practice or clinic and serve as the provider component of a PPO.

—A group of providers also could establish an entire PPO by going into the financing and underwriting business (the latter could be accomplished through a joint venture with an insurer).

—*Maricopa* tells us that simply performing certain administrative functions, such as peer review and claims adjustment, does not take joint price setting activities out of the *per se* category of antitrust violation.

V. Summary and Conclusions

The antitrust laws do impose limits on the ability of physicians to engage in joint fee setting and to employ unfair tactics to discourage or penalize competitors. At the same time, antitrust does not favor one method of payment or one type of physician organization over another. Rather,

it is directed toward preserving open and fair competition in the market for health services.

The doctrines and theories of traditional antitrust analysis are expansive and flexible enough to deal with new forms of physician payment that have already been introduced as well as those that are still a gleam in someone's eye. As in other antitrust matters, the following concerns and questions will be addressed if any of the new payment methods are subject to antitrust scrutiny:

—What are the probable *effects* of the challenged practice? Will it enhance or dampen competitive forces in the market?

—What is its *purpose?*

—*Who* is involved? Are they competitors or are they buyers?

—*What* is really happening? Is the practice under scrutiny a competitive restraint or is it really ancillary to a larger arrangement that will promote greater efficiency and enhance competition?

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DRGs: A Positive Side to the Ledger

Andrew G. Wallace, M.D. and Phyllis S. Ellenbogen, M.B.A.

IN the fall of 1983, the federal government adopted a prospective payment system to reimburse hospitals for services rendered to Medicare patients. Payment based on prospectively set prices seems likely to be adopted by other third-party groups and may prove to be one of the most significant changes in recent years for health care providers. Because it represents a major change and because it is imposed on us by the external world, it is creating considerable anxiety. Change is always an ordeal and fraught with anxiety; the challenge is to adjust constructively to this important change while preserving those characteristics that are essential and desired in medical practice. The thesis of this editorial is that prospective reimbursement can be viewed as having many advantages to medical practice. We must seize this opportunity to take advantage of its potential benefits for clinical research, education, and patient care.

Physicians are trained to be knowledgeable about the behavior of biological systems, all of which are governed by the principles of feedback control. We have learned about these principles as they affect enzyme systems, cell growth, and the operation of all major organ systems in the body. At another level, we are accustomed to these principles in our everyday dealing with patients and colleagues, who give us feedback that helps us evaluate our relationships.

The implementation of prospective payment systems is simply an example of feedback at yet another level, namely the political level. Whether we are engaged in patient care, in research, or in training, these activities are highly private in character but clearly public in purpose. Because of both the benefits and cost, activities of the medical enterprise are a matter of public policy. Prospective payment is being implemented by the government in response to the health care expenditures that exceeded $300 billion in 1983 and, even more importantly, because the health care bill has been increasing at twice the general rate of inflation for the past decade. In decreasing order of resource consumption, hospitals, physicians' fees and nursing homes represent the major components of the health care bill and hence they are the major focus of the feedback forces that are designed to control the rate of increase of that bill.

Government is the major current initiator of the effort to control health care costs. This is because it pays approximately 40% of the total health care cost and about 55% of hospital costs through its role in the Medicare and Medicaid programs. Business is the second largest participant in paying health care costs through contributions to the health care fringe benefit program of employees. Government and business have formed an alliance in their effort to control the rate of increase of hospital bills.

Prospective reimbursement became a reality in the fall of 1983 when the government passed amendments to the Social Security Act calling for the implementation of a prospective reimbursement system based on diagnostic related groups (DRGs). The bill was passed with remarkable speed and by a heavy majority and will be in effect at all hospitals by July 1984.

The strategy of the DRG-based prospective reimbursement system is basically to change the incentive. With retrospective reimbursement of either charges or costs, the incentive to hospitals has been to do more and as a consequence to escalate health care costs in general. Prospective reimbursement essentially states that the payor, in this case Medicare, will provide a fixed payment for the treatment of a given episode of illness. If the hospital spends more than the payment, it is at risk; if the hospital spends less, it has the opportunity to share with the government in the savings.

The government's prospective payment system is based on prices for each of 467 different DRGs. The DRG is simply a classification system that was developed during the 1970s at Yale and then further tested and refined with the Medicare data base. The system first classifies each episode of illness into one of 23 system-specific major diagnostic categories, based on principal diagnosis. Within each major diagnostic category there are several DRGs. These retain elements of clinical coherence and further divide cases, using such information as the principal diagnosis, secondary diagnosis, whether or not an operating room procedure is carried out, age and discharge status of the patient. Hence, a patient with valvular heart disease treated medically would be in one DRG; another with valvular heart disease who underwent cardiac catheterization would be in a second DRG; and still another with valvular heart disease involving catheterization and surgery would be in a third DRG. Based on past records, average costs per DRG have been calculated and used as a basis for setting future levels of reimbursement for an episode of illness.

The DRG system is not a perfect classification scheme and is often criticized because it was not optimally designed to distinguish between subtleties of severity of illness. Let's look for a moment, however, at some of the assets of the system and advantages that it can represent to a hospital and its medical staff.

First of all, the DRG system will increase substantially the effort that the hospital and the medical staff put into the accurate classification of patients discharged from the hospital. As a consequence, we will have much better data

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regarding case mix for each hospital, for each clinical department, for each division within departments, and for each individual physician. To an extent never before possible we will be able to answer the question, who does what?

The clinical data base upon which the DRG classification system is based will now be coupled to the patient accounting system. Hence, it will be possible to aggregate charges by DRG and to know what the costs were to the hospital during any given year to manage patients within each DRG. This will give the hospital an idea of where its resources are being spent and can provide an important management tool to the hospital and to the medical staff.

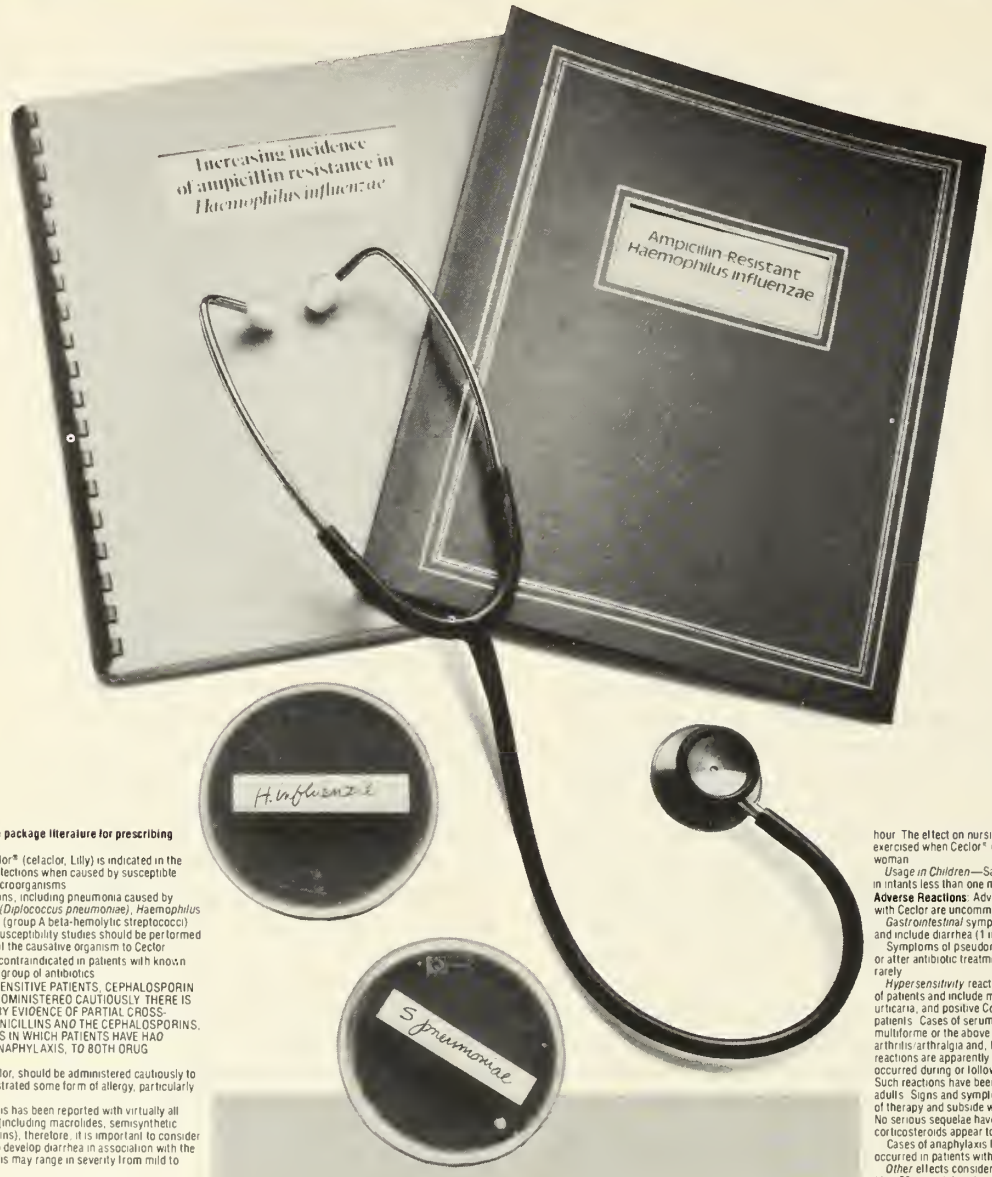
The linking of clinical and financial information for management purposes under prospective reimbursement provides a new opportunity which has not been readily available in the past. Charges for a given episode of hospitalization can be accumulated, categorized by cost center, and reported to the physician more or less in an on-line fashion. It will be possible to know on a daily basis how much has been spent for a hospital room, for laboratory services, for radiology services, for the operating room, for physical therapy, and for any categories of charge within these typical cost center areas. Those charges can then be compared with certain normative data regarding similar cases managed by the same doctor, or at the same institution, or nationally. In this way, financial data can be looked upon as just another laboratory report. In the present climate most physicians are interested in the hospital bill and they are interested in contributing to a reduction in cost as long as that does not compromise their perception of quality patient care. The ability to treat financial data as one would treat any other laboratory variable will provide the doctors with the financial data they seek and will produce a level of awareness regarding expenditures that has the potential of exerting a very favorable influence on the rate of expenditures.

In its simplest form hospital charges can be viewed as a function of both length of stay and the intensity of services rendered a given episode of illness. Thus, efforts to reduce the rate of increase of costs will surely focus on these two principal areas. Hospitals and doctors are now given an incentive to reduce length of stay. Obvious steps can be taken to achieve this objective by focusing on better scheduling during the first 24 to 48 hours of hospitalization, better scheduling and response time for consultations and procedures within a period of hospitalization, and better discharge planning. An important corollary challenge is to make better use of weekend time when hospitalization over a weekend is required. There is no doubt that significant cost savings can be achieved without any threat to the quality of patient services by focusing on such areas.

The intensity-of-services issue represents another important challenge. The new reimbursement system places greater emphasis on clinical research which evaluates benefits and costs of the intensity of services. Most of us would not disagree that there is redundancy within diagnostic testing, that many patients remain connected to physiological monitors beyond the point when clinically useful information can be obtained, that expensive antibiotics are used in some situations in which less expensive drugs would suffice, and that very expensive blood products are occasionally used when whole blood would achieve the same objective. For the last decade or two we have been exposed to the principles of decision analysis as it applies to the diagnosis of the clinical problem or its treatment. There is now a financial incentive to augment that type of clinical research and to apply it in clinical practice.

The circumstances described above demonstrate a new shared purpose between the hospital and its medical staff. The hospital and its information system can become a research resource for the clinical staff and the hospital can become an arena for the clinical staff to implement the results of operational research. We believe that patient care and teaching will benefit from this approach and that cost savings will be a dividend of the effort. If hospitals and their medical staffs can work together and if the new prospective payment system and its related classification scheme can be viewed more as an asset than a threat, objectives can be reached that are in the mutual interest of clinical practice, training, and cost control.

An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

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Brief Summary Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor® (cefaclor, Lilly) is administered to a nursing woman

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

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*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[4]

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Some Reflections on the Relationships Between Universities and Industry As They Influence the Evolution of the Medical-Industrial Complex

Stuart Bondurant, M.D.

THERE is an evolving relationship between American universities and industry of which the relationship between schools of medicine and industry is an important subset. Since this medical industrial complex is a significant influence on American medical schools and on American industry and since it will likely influence both medical education and medical practice, some of the developments and events deserve recognition and reflection. Most research universities and research intensive medical schools have had a variety of relationships to industry for many years. Since our universities and our medical schools are a principal source of new knowledge in our society and since new knowledge is today the economic equivalent of a new continent 400 years ago, it is to be expected that there will be great social value in coupling the sources of new knowledge to the business and industrial machinery that applies the new knowledge. I believe that our national interests are best served by a coupling of the generation of knowledge in our universities and medical schools with the application of knowledge in business and industry provided that the rules of the relationships between universities and industries are such that the values and integrity of both parties are respected and preserved. Among the universities and the medical schools of the United States today, there exists a large range of different relationships with industry and there is a rapid change in the nature of many of these relationships. Some institutions, especially those that are not research intensive, have very few relationships to industry of any kind. Others, both public and private, are building new and different relationships on a base of more than a half century of experience in these relationships. Most institutions fall between these extremes and are now developing patent policies, guidelines for faculty involvement with industry, and programs often being called "technology transfer." Enlightened leaders of industry are negotiating arrangements that seem responsive to the needs of the academic partner.

As the nation's medical schools both public and private broaden their relationships with industry, their students and faculty will be influenced by these relationships. For this reason it is worth considering briefly some of the issues that surround these relationships and are now being addressed in various ways in different institutions.

From the School of Medicine, University of North Carolina, Chapel Hill 27514.

From the perspective of the university and the medical schools, the most important issue can be summarized as that of academic integrity. The very keystone of the academic world is the commitment to an unfettered search for truth and unfettered dissemination of information. The requirement of industry to focus the search and to control the dissemination of knowledge must be reconciled with the fundamental academic value. Most agree that there are ways in which this can be done given the autonomy and scope of the university and its faculty.

A second requirement for academic integrity is the unqualified commitment of the faculty to the purposes of the institution. Insofar as the purposes of the sponsoring industries are not congruent with the purposes of the institution, academic integrity is challenged by the relationship. Again, most believe that there are ways in which the relationship can be defined such that the commitment of the faculty to the purposes of the institution is not compromised.

Third, academic integrity requires that the students perceive that their interests are not compromised within the purposes of the institution.

Fourth, academic integrity requires that the supporters and the sponsors of the institution have confidence in the financial integrity of the institution such that it has not been "bought."

Fifth, academic integrity requires that the institution be recognized as having a high order of competence in its fields of interest and that it is a fertile source of creative scholarship addressed toward important and nontrivial issues. Insofar as the interests of industry may be directed toward short term and highly specific work of little general relevance, the academic institution loses integrity by sacrificing its commitment to scholarship to these goals of industry.

Sixth, academic integrity requires that the educational programs of the institution extend reasonably to the leading edge of the disciplines taught as understood currently. By bringing fundamental and applied questions at the edge of the disciplines into the academic world, relationships to industry can help to enhance academic integrity.

I can speak less knowledgeably of the issues that are of concern to industry. Among these issues, however, are the fiduciary responsibility of the management to the stockholders which means that the ultimate purpose of the corporation must be served by every corporate commitment.

The issue of property rights in the knowledge or materials produced as a result of a relationship between industry and the university or medical school is a part of every such relationship. This is especially true when there are multiple sponsors of a program as, for example, in a state institution where a research program is jointly sponsored by the federal government and one or more industries. All parties prefer that the issues of property rights be as simple as possible and this fact tends to limit participation and collaboration within the institution contrary to the classical values of academe. A third issue for industry is that of ethics and corporate behavior in working with universities and medical schools which have different practices and principles. Some industries have in effect adopted the principles and practices of the universities and medical schools for the purposes of their dealings with the universities and the medical schools while other industries have applied to the medical schools and universities the same business practices they would apply to a competitor or a subcontractor.

A set of issues concerns the relationship of faculty to the medical schools and universities as their relationships to industry change. At the heart of these issues are the definitions of conflicts of interest and conflicts of commitment. These issues are illustrated by the many examples of faculty ownership or officership in corporations working in fields related to the work of the faculty member in the university. Short of ownership or officership by members of the faculty, the role of the faculty as consultants to industry, including the amount of time spent and the terms and conditions of the consultancies, bear upon the effectiveness with which the faculty can fulfill their responsibilities to the medical school or to the university.

The foregoing list of issues is imposing. They are being addressed with apparent success by a number of institutions in a number of different ways.

The research enterprise of this nation has evolved to be based largely in the universities. As compared with basing biomedical and other research in freestanding research institutes, placement in the universities and medical schools has the substantial potential advantage of better assuring appropriate brain power to further the research enterprise in generations to come. A principal disadvantage of siting the research enterprise largely in the nation's academic institutions is the attenuation of the relationship between research and application. In my view, it would be a mistake to resist the growing articulation of the teaching and research enterprise of the nation's medical schools with industry. Rather, just as our schools have in times past risen to the challenge of helping to assure access to health care and the availability of quality health care, I believe that we should now accept our responsibility to strengthen the relationships and pathways that bring new knowledge into practice through purposefully structured relationships between industry and universities and medical schools.

North Carolina Medical Journal

Features for Patients April 1984

Learning Disability

Robert J. Thompson, Jr.

Why can't Susan learn?

Why can't Jahnny read?

Understanding why children have difficulty with educatianal tasks and finding ways to help children learn present major challenges to parents, teachers, and health care praviders. There can be little daubt that a child's ability ta learn influences his ar her adjustment in aur saciety. Thase who have difficulty in learning can experience cansiderable stress and their difficulty can be as much af a handicap as any ather handicap. If the learning difficulty becames chranic, the persan can indeed be disabled.

Difficulties in learning can arise for numerous reasons. Some are associated with disarders af the brain and central nervaus system. Children with mental deficiency ar mental retardatian have difficulty in learning because af deficits in intellectual functianing. Children wha are blind ar deaf alsa experience learning difficulties related ta the impairment af their visual or auditory capabilities. Children with majar emational or behaviaral prablems related ta enviranmental factars may alsa demanstrate learning difficulties that arise from being distracted, preaccupied ar otherwise "unavailable" ta profit fram customary educational experience. Far some children, learning difficulties are related ta a canstellatian af poar health and educational opportunities.

Children with learning prablems that are assaciated with ar "secandary" ta ather disarders ar situatians have variaus interventian or remediation pragrams available ta them. Far example, there are special educatian pragrams to help children with mental retardation, blindness, ar deafness learn ta the fullest extent af their capabilities.

Gradually aver the last 20 years, there has been an emerging recognitian af the existence af children wha da nat learn narmally but whase learning prablems are nat secondary ta ather knawn disorders. With these children, there is a discrepancy between learning perfarmance and presumed capacity. These children seem ta have peripheral and central nervaus systems that functian praperly and ta have adequate appartunity far learning, but they da nat learn according ta expectatians. Fram these gradually emerging recagnitians and differentiations has came the cancept af the child with a learning disability, that is, a child whase learning difficulties are nat "secandary" to anather disarder, but are "primary."

While the cancept af learning disability appears clear, determining what a learning disability is, what causes it, what ta da abaut it, and wha is and wha is nat learning-disabled has generated much canfusian and cantraversy ta the cansternatian of parents, clinicians, legislatars, and researchers. Some af the confusian has arisen from the multidisciplinary nature af the field. Psychalagists, speech and language clinicians, special educatars, pediatricians, physical and accupational therapists, neuralagists, aphthalmalagists, aptometrists, and lawyers all have contributed their diverse disciplinary perspectives and techniques. Alsa cantributing to the canfusion has been the lack of an agreed upon definitian, classificatian system, and diagnastic criteria. In a recent review af 408 studies, far example, it was discavered that aver 1400 diagnastic techniques had been used to select ar describe learning disabled children![1] Finally, it aften appears that there must be at least as many remediatian pragrams or treatment appraaches far the child with a learning disability as there are diagnastic appraaches. Twa paints abaut which there has been particular canfusion have been the definitian and the rale af emotianal prablems in learning disabilities.

From the Division of Medical Psychology, Duke University Medicol Center, Durhom 27710.

How Is Learning Disability Defined?

Numeraus definitians of learning disabilities have been propased. Same af these definitions have been incarporated into federal and state legislatian affecting services far handicapped children. In the 1973 cangressianal hearing on the Develapmental Disabilities Act, learning disabilities were defined as:

> A disarder in ane ar mare af the basic psychalagical processes invalved in understanding ar in using language, spoken or written, which disorder may manifest itself in imperfect ability ta listen, think, speak, read, write, spell, ar da mathematical calculatians, and such disarder may include such conditions as perceptual handicaps, brain injury, minimal brain dysfunctian, dyslexia, ar developmentol aphasia, but such term daes nat include learning problems which are primarily the result of visual, hearing, or matar handicaps, or mental retardation, ar ematianal disturbance ar af enviranmental disadvontage.[2]

A similar definitian was included in Public Low 94-142 — The Educotion for All Handicapped Children Act of 1975 which ossures a free and appropriate educotion for oll hondicopped children. In oddition to the number of definitions ond lack of consensus, there are ather problems associoted with the definition. Both the concept and the definition hove broodened over the yeors resulting in on overly inclusive cotegory thot locks meaningfulness. Many definitions are circulor and exclusionory to the point that they soy more about what a learning disability *is not* than what *it is*. Finally, many definitions hove focused olmost exclusively on deficits within the child to the exclusion of environmentol factors ond the interactian af environmentol foctors with factars within the child.

Some of these concerns were addressed in the definition proposed in 1981 by the Notionol Joint Committee for Leorning Disobilities representing a number af professional organizations:

> Learning disabilities is a generic term that refers to a heterogeneaus group of disarders manifested by significant difficulties in the ocquisition and use af listening, speaking, reading, writing, reasoning ar mathematical abilities. These disarders are intrinsic to the individual and presumed to be due ta central nervaus system dysfunction.[3]

Hawever, this definitian also emphasizes intrinsic factors ta the exclusion of enviranmental factors.

Just as there have been many proposed definitions, there are alsa multiple classification systems to graup various subtypes. Learning disobilities have been classified by area of the problem: dyslexia — reading problem, dyscalculia — moth problem, dysgraphio — writing problem; and by channel af difficulty: auditary perceptual or visual perceptual; and by impaired processes: discrimination, integratian, and sequencing. With various definitions ond classificatian systems, it is not surprising thot estimotes of the number of leorning disabled children also hove varied considerobly from 1% to 4% of the school oge populotion.

While the definitionol problem still exists, odvonces hove been mode in understonding through reseorch thot should provide the foundotion far further systemotic research regarding the noture of leorning disobilities ond their prevention and treotment. First, it is now recognized thot leorning disobility is on umbrello category for o very heterogeneous group of children. Any group of learning disobled children is likely to contoin children who have leorning difficulties becouse of a voriety of problems. Second, o cammon problem in leorning disobilities is one of processing — thot is, using spoken or written longuage. By processing is meont ottending ta, encoding or toking in, staring, decoding, and retrieving infarmotion. Third, the nature of these processing difficulties is as yet imperfectly understood but is thaught ta be related ta structurol abnormolities in the parts af the broin respansible for processing information. Faurth, research effarts are being focused an establishing the manner in which pracessing disabilities actually affect perfarmonce on schaol tasks. Fifth, once the relotionship between processing disobilities and ocademic deficits has been ascertained, remedial strategies that are respansive to individual differences in pracessing skills can be developed.

Learning Disability and Emotional and Behavioral Problems

Far many years there wos o tacit assumption that learning disarders ond emotional problems were related. This assumption influenced bath diagnastic ond interventian pracedures. In many child clinics, it had became habituol ta assume a psychalagical basis for a child's learning problems when na easily recagnizoble arganic basis could be found. Hawever, evidence hos now accumulated obout the influence of neurological os well os psychological foctors in learning problems thot illustrotes the gross inodequacy of conceptualizing leorning disorders os simply o manifestotion of on underlying emotional disturbonce.

What hos resulted is o more considered view. Some children with learning problems do exhibit neurotic feors and traits. Some children foil to leorn ond exhibit behovior problems becouse of o primory emotional problem stemming from organic ar environmentol foctors. For other children, the emotionol problems ore secondory and con best be understood os o result of the interoction of inodequotely developed primary skills ond environmental stresses that can interfere with psychosexuol development and odversely influence the child's developing self concept. The probobility thot a learning-disobled child will develop emotionol or behoviorol problems is related to many variables such as

severity and chronicity of the prablems, age, sex, subcultural group, sacioeconamic level, and intelligence. Many learning-disabled children da cope well. Hawever, all learning-disabled children encounter serious obstacles ta adjustment, and their ematianal demonds and stresses exceed thase af mast children.

Learning-disabled children have the same basic needs and drives as other children, such os the need for occeptance, adequocy, campetency, ond mostery, but their handicap sometimes obstructs the satisfaction of these needs ond drives. When this occurs, adjustment is threatened ond emotional and behaviaral prablems may develap. The expressian af these problems is varied. That is, there is no single reactian pattern ar syndrome of behaviar camman to the learning-disabled papulatian.

However, there are some commonalities. Becouse of the cognitive-perceptuol-motor difficulties, the child can be viewed os vulneroble. This vulnerability con leod to leorning ond behavior problems thot influence the reoction of persons in close contoct with the child. Frequently, these significont persons (porents ond teochers) can respond with blome and criticism thot increoses stress and feelings of frustrotion ond tension. Poor self-image con result from foilures and from the feedbock thot the child receives from others. Feelings of inadequacy and o poor self-concept are likely to prolong dependency and immoturity ond the utilizotion of immoture defense mechanisms, such os projection of blome and ovoidonce. This ovoidonce of tasks impoirs motivotion ond causes a further deficit in skills because certoin skills must be procticed to be leorned. Thus, there is o lock of improvement, which perpetuotes this vicious circle.

A number of studies hove used behovior checklists to ossess the noture ond extent of behovior problems with children with educotionol problems which range from those requiring special educotionol progroms to thase wha are "mainstreamed." The findings indicate that the behaviar problems in these special groups are very similar ta those faund in the general populatian and in ather clinical subgroups: persanality prablems, conduct problems, and inadequacy/immaturity. Most studies repart that the special educatianal subgraups have higher levels of all three behaviar prablems than children withaut learning problems. In addition, cantrasts are frequently made with respect to the extent of behavior prablems among subgroups af children requiring special education, such as children with mental retardatian, learning problems, and emotianal prablems. The findings ore nat olways cansistent with respect ta the relative frequencies af each of the three behaviar prablems. However, the studies da reveal higher levels of behaviaral disturbance among children with ematianal prablems thon omong those with primory leorning problems (learning disobled ond mentally retorded). Those with primory leorning problems demonstrote higher levels of behoviorol disturbonce than children without leorning problems but differences between mentolly retorded ond leorning disabled subgroups ore inconsistently reported.

Views about the ossociotion of leorning disobilities ond emotional ond behaviorol problems influence service programs. There hos been o reliance upon cotegoricol models bosed upon on either/or theory of etiology; thot is, conceptuolizing schaol molodjustment either os o leorning problem or as on emotionol problem. This hos resulted in some benefits, such os closses for leorning disobled ond for emotionolly disturbed children. However, the underlying continuum has been obscured.

What has been needed is o model thot integrotes an understonding of personality voriobles with other functionol impoirments. The model of secondory emotionol problems os outlined obove with its focus upon environmentol foctors interocting with vulnerabilities is ane madel that offers the potential for develaping pragrams thot meet all the needs, primary and secondary, af the child.

What is Dyslexia?

Children experiencing primary learning prablems in reading are frequently referred to as dyslexic. Thase wha have learned ta read with little difficulty take reading pretty much far granted. Reading is, however, a very camplex cagnitive-auditary-visua-spatial pracess. It invalves integratian af several input, autput, and mediating processes, visual perceptian and discrimination and crass-madal integratian — the translatian of visual symbols into meaningful auditary equivalents.

The twa frequently used reading instructian methods ore based an the visual and auditory pracesses underlying reading. The whale-ward ar "look-soy" technique is bosed on a visual whole. The phonetic technique relies upon the child's onolytic ond synthesizing obilities in separoting words into their phonetic components.

Any failure to leorn or retordation in leorning this complex reoding process can be considered os dyslexio. Reoding retordotion occurs whenever there is o significant discrepancy between the octuol reoding level of o child ond the reoding level expected based on thot child's mentol oge. The amount of discrepancy typicolly required to be considered dyslexio is 2 years.

Severol reseorchers hove identified subgroups of dyslexic children based on functionol processing difficulties. One subgroup of dyslexic children comprises those who hove difficulty in symbol-sound integrotion resulting in difficulty developing phonetic word onalysis-synthesis skills. Another subgroup of dyslexic children has a primory deficit in the obility to perceive letters ond whole words os whole visuol configurotions. There is onother subgroup of dyslexic children who demonstrate deficits in both phonetic word onoly-

sis-synthesis skills and visual perceptual skills. Evidence suggests that the phanic based deficits are mare frequent than the visua-perceptual deficits.

Separating children inta groups according ta the type af pracessing difficulty they exhibit allaws the develapment af useful pracedures specific ta each group. Far example, far the child with phanetic-based dyslexia, phanetic skills will be difficult ta learn and whale word techniques cauld prave ta be mare effective. Far children with visual dyslexia, a phanetic appraach can be used. Far children with both phanetic and visual dyslexia a tactile-kinesthetic approach may be necessary.

Apprapriate and meaningful subgraup farmation based an causal and functional findings provides the appartunity to develop deficit-specific treatment appraaches and to accumulate knawledge abaut what warks best with whom. Much af the pragress in this area will af necessity be gained thraugh trial and errar. Theary will na doubt guide the explaratian but much is ta be gained fram systematically studying haw successful teachers af learning-disabled children achieve their successes so that these remediatian skills can be taught ta ather teachers.

Services for Learning Disabled Children

With learning disabilities as well as ather disarders those affected with the disorder require attentian naw even thaugh we still have quite imperfect understanding. Service pragrams have evalved ta meet the needs af children with learning prablems and their families. If parents are cancerned abaut their child's averall level ar rate af learning ar abaut specific learning prablems in reading, writing, or math, these cancerns shauld be braught ta the attentian af their school system and their physician. Mast schaal systems have screening and/or educatianal diagnastic services available to help identify academic problems. Pediatricians and family physicians are increasingly attending ta learning and behaviaral prablems in children as well as ta custamary health prablems. The pediatrician ar family physician can play an essential role in praviding far additianal diagnastic assessment and in helping ta implement and caardinate an averall remediatian plan.

With a suspected learning prablem, obtaining a camprehensive multidisciplinary evaluatian invalving a team appraach af physicians, psychalagists, speech and language clinicians, special educators, and physical and accupatianal therapists is essential. This comprehensive appraach is necessary ta determine the level and adequacy af the functian of variaus systems in the child and his/her family and school environment that are invalved in the learning pracess. The results af this camprehensive evaluation pracess serve as the basis far a remediatian plan that will involve the educatianal services af the schaal and result in an individual educatianal plan (IEP) far the child. This IEP is develaped by the schaal system in canjunction with the parents and sets specific gaals and interventian strategies. Depending upan the results af the camprehensive multidisciplinary assessment pracess, ather services, such as speech and language therapy, medicatian ar psychatherapeutic assistance may alsa be needed. If sa, it is important far all these services to be coardinated and far the averall treatment plan ta be manitared in terms af the pragress being achieved. Periadic reevaluatians may be necessary ta update the interventian plan. The pediatrician ar family physician can be helpful with these coordinating and manitaring tasks.

Narth Caralina is fartunate in having a number af resaurces available ta families far comprehensive multidisciplinary assessment af children with learning disabilities. This type af service is available at the majar medical centers such as the Duke Develapmental Evaluatian Center which is funded by the Narth Caralina Department af Human Resaurces through a cantract with the Department af Pediatrics at Duke University Medical Center. In additian, the Narth Caralina Department af Human Resaurces supparts a system af 18 ather Develapmental Evaluatian Centers acrass the State where camprehensive multidisciplinary evaluatians of children with suspected develapmental ar learning problems can be abtained. Further infarmatian abaut services far learning disabled children can be abtained fram yaur lacal schaal system and from the Develapmental Evaluatian Center that serves yaur caunty. Information can alsa be abtained fram the North Caralina Associatian far Children and Adults with Learning Disabilities, P.O. Bax 585, Wilmington, NC 28402, 919/763-0658.

Narth Caralina is fartunate also in having a number of remediatian resaurces available for children with learning disabilities. There are two primary saurces far these services. The public schaal systems have specially trained teachers wha pravide remediation for learning-disabled children thraugh special classes and through learning disability resaurce experiences. Anather saurce af remediatian is thraugh the services offered by specific learning disability centers such as the Hill Learning Develapment Center in Durham.

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Developmental Evaluation Centers in North Carolina

Develapmental Evaluatian Center
5 Frederick Street
Asheville 28801
704/254-8876

Developmental Evaluation Center
N.C. State Emplayees' Credit Union
Boone 28607
704/264-1280

Divisian of Disarders af
Develapment and Learning
Biolagical Science Ctr., Bax 523
University of Narth Caralina
Chapel Hill 27514
919/966-5171

Develapmental Evaluatian Center
3500 Ellingtan Street
Charlotte 28211
704/372-7790

Develapmental Evaluation Center
304 Winecoff Schaal Road
Concard 28025
704/786-9181

Developmental Evaluation Center
Western Caralina University
Cullawhee 28723
704/227-7490

Develapmental Evaluatian Center
Duke Medical Center
2213 Elba Street
Durham 27705
919/684-5513

Develapmental Evaluation Center
P.O. Bax 189
Elizabeth City 27909
919/338-2167

Develapmental Evaluation Center
3403 Melrase Road
Fayetteville 28304
919/486-1605

Develapmental Evaluation Center
2311 W. Cane Blvd., Suite 143
Greensboro 27408
919/282-1100

Developmental Evaluation Center
East Caralina University
P.O. Bax 2711
Greenville 27834
919/757-6921

Develapmental Evaluation Center
Landco Bldg., 121 N. Sterling Street
Marganton 28655
704/437-2947

Develapmental Evaluatian Center
Homestead Sq., 2717 Neuse Blvd.
New Bern 28560
919/633-0775

Develapmental Evaluation Center
3325 Executive Dr., Suite 110
Raleigh 27609
919/733-6895

Develapmental Evaluation Center
111 Medical Arts Mall
Racky Mount 27801
919/443-8858

Develapmental Evaluatian Center
Prafessianal Ctr. No.
804 N. Lafayette Street
Shelby 28150
704/482-4416

Developmental Evaluatian Center
107 E. Ashe Street
Wadesbora 28170
704/694-5186

Developmental Evaluatian Center
1920 South 16th Street
Wilmingtan 28401
919/762-1744

Develapmental Evaluation Center
Bowman Gray School of Medicine
3325 Silas Creek Parkway
Winston-Salem 27103
919/765-9916

Hill Learning Development Center
An Approach to Remediation of Learning Disabilities

Margaret Sigmon, M.Ed. and Wendy Speir, M.Ed.

The Hill Leorning Develapment Center (LDC) was established in 1977 to pravide on intensive program to students with specific learning disabilities. Begun as an adjunct ta the existing pragrams of Durham Acodemy, the LDC was dedicated to founder George Wotts Hill in 1980 and became an integral part of Durhom Academy. It is naw one af the five schools that compose the Academy structure.

The purpase af the LDC is to pravide the intensive, specialized, and supportive educatian needed by learning disabled children to gain ocademic skills and learning strategies thot enable them ta return ta the regular classroam as successful, independent learners. Thraugh systematic multisensary instruction, the LDC strives to assist each individual in realizing his/her patential through develaping strengths, remediating weaknesses, ond experiencing success.

In addition, the LDC provides suppart and assistonce ta porents through warkshaps, educational programs, and frequent cammunicotian between home and schaol. The Center is alsa cammitted ta pramoting public awareness af leorning disabilities and to serving the community through lectures, teacher-training warkshops, and consultatian with persannel in the area schaols. On-gaing training is pravided ta the LDC staff members in the olternative teaching methads thot allow mastery af basic skills. The LDC caaperotes with nearby universities in praviding sites far observation ond placement af students in teocher-training programs.

From the Hill Learning Development Center, 3130 Pickett Road, Durham 27705.

The Admissions Prôcess

Students applying ta the LDC pragram must have been diagnosed as learning-disabled by a licensed psychalagist. Such evaluotians may be carried aut by psycholagists within the schaol system or in private proctice. Diagnasis as learning-disabled is based on average ar abave average intelligence with a discrepancy between aptitude and current achievement in the clossroom and na primory emational disturbance. Students enrolled in the LDC program may demanstrate difficulty in reading, spelling, mathematics, handwriting, arganization af written language, ar any combination of these oreas. These learning disabled students may or may not quolify for resource help in the public schools according ta the North Caralina state guidelines.

The applicatian pracedure requires that farms be completed and returned by the parent, physician, psychalagist, schaol personnel, and teachers ar clase friends wha know the child autside af the classraom. An educational evaluatian is conducted at the LDC in arder ta meet the opplicant, assess academic achievement, and analyze strengths and weaknesses in the learning pracess.

The Academic Program

Approximately seventy students (preschaol thraugh high schaal) ore enralled in classes at the LDC far a portian af the school day while alsa attending lacal public ar private schools for the remainder af the day. Full-day placement at the Center is pravided far a limited number of elementary students when deemed appropriate.

Students in preschaal through high schaol may attend the LDC to earn credits in basic language arts and math. Juniar and senior high students are alsa affered instruction in a fareign language, algebra, geometry, English grammar and campasition. Transfer credits and grades are issued far students in grades seven thraugh twelve.

Enrallment at the LDC is generally shart-term. In mast instances necessary remediatian may be accomplished in one-and-o-half to twa years and students are able ta return ta their regular schaols an a full-time basis. Emphasis may be on either remediatian of basic skills or campensatory educatian.

Based on informatian acquired fram psychalogical ond educatianol evaluations, specific instructional objectives are written far each individual. These abjectives, similar ta an IEP ar Individual Educational Plan in the public schools, constitute the curriculum far that individual ond are revised each semester based an the pragress made during that period.

Certified teachers, wha hove participated in extensive in-service training at the LDC, work with three students in o graup wha have been corefully selected an the basis of skill level, age, and campotibility.

Progress is reparted throughout the schaal year in the form of instructional objectives, written interim reports, grades, ond scares fram pre- and past-testing. Parent conferences ore scheduled at least twice during the schaal year and may accur mare frequently upan request.

Typically, the half-day pragram consists af twa haurs of instructian in the language arts area and ane hour af mathematics instructian. Language arts is separated inta decading

(reoding) ond encoding (written language) classes. Decading cansists af word attack, oral reoding, ond reoding camprehension while encoding includes spelling, hondwriting, and campositian.

While na single opproach to teaching reoding is used exclusively, a highly structured phonetic system (based on the Orton-Gillingham approoch) hos been porticularly successful in teaching students to read, write, and spell.

Math instructian fallows o format similar to languoge arts instructian since the LDC uses o languoge based approach where wark with all symbols is cansidered a language process. Math class includes memarization of bosic focts and computational pracedures, computation practice including timed tests, and opplication of these skills in word problems.

The remediatian opproach ot the LDC involves using multisensory teaching techniques in o very structured environment designed ta remave the mojor obstacles to learning such as visual and auditary distroctians. While students wark in small groups af three, each student has an individuolized curriculum ta provide instruction in the areas where he demanstrates skill deficits. In addition to farmal assessment af achievement ond skill mastery, teachers use a test-teoch-test approach to infarmally ossess what a student hos learned and to begin teaching ot a point appropriate far the individual student. Smoll units of infarmation are presented sequentially and procticed until an automatic correct respanse can be given far three ta five cansecutive doys. Due to memary deficits in many learning disabled students, averleorning oppears ta be necessary to ensure long-term retentian.

Class time is structured to provide review of moteriol recently learned through bath oral ond written drill, presentation of new moterial, applicatian of new skills, ond integratian af new information with previausly acquired skills. Homework is ossigned doily in each class ta provide odditianal practice of skills learned in class. Classes are designed to maximize opportunities far student response ond success experiences. An incarrect answer given by a student is immediately corrected and reinforced sa thot the student is more likely to remember the correct respanse. Student-teacher interaction focuses on proise and pasitive reinforcement af carrect answers ar approximatians af the correct respanse.

Additional Programs

In oditian to the regulor doy pragrom during the schaol year, the Center offers a study holl program twa nights per week for students in grodes five through twelve. Study Hall is held Mandoy and Wednesday evenings from 7:00 ta 9:00 p.m. and is stoffed by two members of the LDC faculty. The student/teacher ratio does not exceed five students per teocher. The pragrom is intended to provide assistance in completing homework ossignments through organization of moterials, drill ond review, and instruction in study skills.

The LDC olso offers a six-week Summer Progrom far three hours per day following the same instructionol progrom as the academic year. The Summer Pragram pravides on opportunity for students alreody enrolled in the school program to cantinue instruction thraughout the summer and therefare prevent the regression of skills that can occur withaut daily practice. The pragram is also intended to serve students who ore not enralled in the schaol yeor program but wha moy benefit from an intensive remediation progrom during the summer befare returning to their regular clossroams in the foll.

Aging and the Skin

Claude S. Burton, M.D., Peter Heald, M.D., and J. Lamar Callaway, M.D.

The heart weors out in o hundred yeors, the kidney losts obout 150. But the skin never wears out. Whoever heord of onyone dying of old skin? Skin is continuolly in the process of rejuvenotion. Nevertheless, there ore chonges thot occur to our skin that olter its oppeorance and performonce. Wrinkles, thinning, changing pigment, and chonge in elasticity ore commonly ossocioted with oging. These ore highly visible clues thot reflect o more generol process. The morket for products to core for these chonges is enormous. Billions ore spent onnuolly. A porodox exists in thot most of the money is spent where the leost benefit con be expected. Most of the products ore opplied after the domoge is done. In this cose an ounce of prevention is truly worth a pound of cure.

There is no preporotion or formula known to reverse aging of the skin. Much of what we coll oging is premoture deteriorotion due to trauma from the sun. To illustrote this point we osk our potients to compore the "oged skin" on their honds ond foreorms to skin that is just os "old" in the oxillo or buttocks oreo. In these oreos with little sun exposure patients ore surprised to see how "youthful" their skin really looks. Unfortunately, though the convincing is eosy there is little thot con be done ot this point to reverse the domoge. Chonges due to sun ore cumulotive ond much of whot we see in o person's skin ot oge 50 reflects sun exposure os o child.

There are many reosons other thon vonity to protect our skin. The skin is o borrier ogoinst on otherwise hostile environment. Skin thot is sun domaged doesn't lubricote normolly ond is subject to drying ond crocking. This is the result of sun domoge to the glandulor elements in the skin ond domage to the basol cells which replenish the epidermis. Sun damoged skin is thin, frogile, ond heals poorly. The elostic substonce in the tissues is exquisitely sensitive to ultroviolet ond thermal rodiotion.

The solution should be obvious. We must protect our children from the eorly rovoges of sunlight. With the use of common sense, ond sunscreens, our children will hove the chonce of youthful skin oll of their lives.

For odults, sunscreens ore useful in preventing further domage ond should reduce the incidence of skin cancer. At this lotitude doily application in the spring ond summer should become o hobit like brushing our teeth. Since domoge is usually present, odditionol core is often needed. Aged skin lubricotes poorly and will often require the topicol opplicotion of o moisturizing agent and the ovoidonce of soop. Vitomin C supplementotion in modest doses (1-2 g doily) is recommended to promote the integrity of the collogen in the skin. Collogen is the leather thot mokes up the bulk of skin. The thinning of skin with age is lorgely the result of diminished collagen. Vitomin C levels tend to be lower in elderly persons ond in mony coses ore near the levels seen in scurvy! It is expected thot Vitomin C will retord the thinning process ond promote proper wound heoling, ond it moy olso improve the easy bruisobility noted with oge. Studies to confirm the usefulness of this recommendation ore underway and preliminory results look promising. It is no longer true that nothing con be done obout "aging."

From the Department of Medicine, Duke University Medical Center, Durham 27710.

4-Aminoquinolines Can Be Dangerous to Your Health: Chloroquine (Aralen) Intoxication

Ronald B. Mack, M.D.

WHAT in the name of Mithridates (Mithridates VI was a king, legends relate, who claimed he had discovered an antidote for every poisonous substance. Thus the archaic term "mithridatic" referring to an antidotal or protective mixture) are the 4-aminoquinolines? I asked some of our medical students and got such answers as: "Do they take unleaded gasoline?" "Four people who acquired AIDS from using the same comb." "An English rock group who recently sold a million records." These were the good answers.

During World War II (surely you remember the Big One) the antimalarial agent quinine was no longer available to the forces that were trying to overcome Hitler, Mussolini, Tojo and their minions. Quinine is the major alkaloid of cinchona bark (which is indigenous to certain areas of South America). Cinchona alkaloids were the only chemotherapeutic agents available for the specific therapy of malaria until the 1930s. In the third decade of this century *quinacrine* was introduced as an antimalarial agent. It soon became apparent that quinacrine was superior to quinine. Quinacrine was not an ideal drug, however, as it did not apparently act as a true prophylactic against malaria and did not cure benign tertian malaria. World War II provided a very strong impetus to develop an antimalarial that was a more effective and less toxic drug. By the time the war ended, *chloroquine* was developed and found to be a most promising chemical to combat malaria. Nevertheless millions of doses of quinacrine (Atabrine) were reluctantly ingested by Allied servicemen especially those serving in highly endemic malaria areas such as Africa and the South Pacific. (Will any of us ever forget the terribly bitter taste of Atabrine and the ugly yellow skin color that resulted from its use? Ugh!! It makes the food in the hospital cafeteria taste like Maxim's by comparison.)

So you might ask, why an article on chloroquine? Surely you don't see much malaria in North Carolina. Why is the author bothering us with war stories and a group of drugs that the average health care professional in our State does not need to know about? I submit to you that this group of drugs is being used in North Carolina and against some fairly common diseases at that. *Giardiasis* is probably the most common parasitic cause of diarrhea in America and is the most common cause of parasitic-induced malabsorption in this country. The treatment of Giardiasis is either quinacrine or metronidazole (Flagyl). *Rheumatoid arthritis, discoid lupus erythematosus,* and *extraintestinal amebiasis* are other diseases for which chloroquine is utilized and certainly plenty of patients with these diseases exist in our fair State.

So what's the big deal here? Is chloroquine *that* toxic in overdose? You bet your bippy it is!! (I haven't been this excited since Margaret Thatcher showed her ankles in *People* magazine.) Chloroquine overdose kills, is commonly fatal in children, and the entire time course from ingestion to death can be short indeed. Many authors consider a single dose of 1.5 grams of chloroquine base to be toxic in an adult and a single dose of 2.0 grams to be potentially lethal. For children and adults, 35-50 mg/kg of chloroquine base may well be a fatal dose. Chloroquine phosphate USP is the name of this drug as you write it in a prescription but only 60% of it is the chloroquine *base*. The clinical features of an acute chloroquine poisoning episode are classically divided into three categories: *neurological, respiratory,* and *cardiovascular*.

Neurological adversities include drowsiness, often the earliest feature, photophobia, diplopia, and seizures. Seizures can be a presenting sign but are just as likely to be seen pre-terminally. *Respiratory* difficulties are quite common and variable but include quite rapid superficial breathing all the way up to and including sudden apnea and respiratory failure. As if these problems are not bad enough, the worst is yet to come: *cardiovascular manifestations* are awesome in chloroquine intoxication and most authorities submit that the acute toxic effects of chloroquine are mainly exerted on the heart. This drug is a powerful cardiotoxin; it reduces the excitability and conductivity of cardiac muscles similar to the effects observed with quinidine. The cardiovascular effects of chloroquine in overdose include vasodilatation and hypotension (a sudden fall in blood pressure is a very characteristic feature of this overdose), and of course arrhythmias and *cardiac arrest*. The quinidine-like EKG abnormalities include widened QRS, inverted or flattened T waves, and ventricular tachycardia. Myocardial toxicity and arrhythmias are probably the cause of death in chloroquine poisoning rather than vasomotor, respiratory, or neurologic insult.

Chloroquine is quite rapidly and almost completely absorbed from the GI tract. The drug is rapidly taken up by the tissues where it is deposited in quite significant amounts. Approximately 55% of chloroquine in the plasma

is bound to nondiffusible plasma constituents. According to autopsy data the concentration of chloroquine in the heart, liver, kidney, and lung greatly exceeds concentrations in the blood. Of interest is the fact that brain concentrations are similar to blood concentrations. The volume of distribution (V_D) of this drug is quite high. (Readers who like to think ahead will quickly surmise that because most of the drug is not in the blood the prospect of removing it via extracorporeal mechanisms is slim to none.)

It cannot be emphasized too strongly than an acute chloroquine ingestion is a "fire engine red" emergency first class. This is especially true when a child is involved. Time is not on your side here; death occurs within a few hours after ingestion of a toxic dose. Chloroquine phosphate (Aralen) is supplied in tablets containing 500 mg, 300 mg of which is the *base*. Thus a 2-year-old environmental investigator weighing 28 pounds (12.7 kg) needs to ingest only 2 such tablets to achieve mortality. Even the ingestion of 1 such tablet has been reported to cause death in an infant. Now that's frightening!! What are we really talking about here? — we are talking about a medicine used throughout our State for various diseases that has a narrow margin of safety between therapeutic and toxic doses, a rapid onset of an extremely toxic syndrome with fatal outcome not uncommonly, with no specific antidote or antagonist and death resulting in one to three hours due to cardiorespiratory failure.

The treatment of chloroquine overdose is, to say the least, meager. As stated previously there is no specific antidote to counteract the acute toxicity — no naloxone or methylene blue or BAL or such. Obviously gastric emptying, if performed early enough, could be life-saving. The drug is absorbed quite rapidly, as noted; therefore administration of syrup of ipecac in the home to children 1 year of age or above very very shortly after ingestion is the way to go. (Children less than 1 year of age are generally better off getting ipecac syrup in an emergency room where they can be monitored by professionals.) Gastric lavage can be implemented as an alternative if done as soon after ingestion as possible. If symptoms have already appeared by the time you see the patient, gastric emptying may be a futile gesture. If the patient ingested the chloroquine on a "full" stomach, i.e., after a meal, the drug's absorption is slowed considerably and gastric emptying is surely indicated. After gastric emptying has been accomplished, administration of activated charcoal and a saline cathartic might decrease the prospect of further chloroquine absorption. Of course you must support respiration. The other complications are treated in a supportive fashion — using vasopressors to counteract hypotension, diazepam for seizures, a ventilator, a cardiac pacemaker, and so on. Some of the literature, including recent articles, talk about the use of urine acidification to increase the renal excretion of chloroquine. However, in my opinion, the data are soft and this method cannot be endorsed with the limited data that are available.

Quinacrine (Atabrine) is a drug similar to chloroquine (an acridine compound consisting of a substituted 4-aminoquinoline radical linked to a benzene ring) and can cause nausea, vomiting, and diarrhea when taken in overdose, and when consumed in large overdose can cause a cardiac death similar to chloroquine. Because of the increase in the discovery of patients with giardiasis (especially children), more and more of this medication will be available to preschool taste experimenters. Beware also of patients with glucose-6-phosphate dehydrogenase-deficiency who receive quinicrine — this combination can result in acute hemolysis. Atabrine, even in therapeutic dosage for giardiasis, commonly causes patients to acquire a very yellow hue to their skin. This yellow pigment is concentrated in the epidermis in concentrations 100-200 times that of plasma. A recent paper[1] recommends examining the patient's palms, fingernails, and urine with a Wood's lamp. If the patient has been ingesting quinacrine these areas emit a brilliant yellow green fluorescence, and the Wood's lamp helps you to distinguish this cause from other diseases including congenital cowardice.

This group of drugs is particularly scary to me and I hope to the reader. I have resolved not to get malaria or giardiasis or rheumatoid arthritis or discoid lupus or any such craziness. The way to achieve this, I am convinced, is to try the Mack Diet which in my opinion is superior to the Pritikin Diet, Weight-Watchers, Cambridge Diet, Slim Fast Diet to name a few. The diet is simple and easy to prepare — pasta in any form at least twice a day. No disease could possibly attack you after you have been on this diet for a while; there would be no place for the illness to land. I am convinced that spaghetti is anti-inflammatory.

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Moonlighting: A Practice to be Encouraged?

William S. Kelly, M.D. and Penny C. Sharp, B.S.

RESIDENTS who moonlight, i.e., engage in extramural professional activity, are almost universally enthusiastic about its value as an educational experience. Moonlighting is officially discouraged by the Liaison Committee on Graduate Medical Education (LCGME) of the Association of American Medical Colleges, however, as a practice that is "inconsistent with the educational objectives of house officer training."[1] In fact, many institutions do permit residents to moonlight, and faculty members and residency directors are sometimes heard to grudgingly admit that some of their best residents do moonlight. Perhaps the controversy exists because there is virtually no literature that documents what residents do while moonlighting. We present data that document the moonlighting experience of a second year family medicine resident and compare that experience with the residency-based outpatient experience during the same time interval.

Several studies have defined the content of family medicine both in academic and in private practice settings.[2-4] Some interesting differences in the academic and private practice of family medicine have been demonstrated. It seemed likely that there would be marked differences between the patient populations seen while moonlighting and while performing residency-based outpatient medicine even though much of the moonlighting was done in a private family practice setting.

The sample consists of 687 patient encounters. Any given patient may have been seen more than once and may have had more than one diagnosis. Of these, 282 encounters took place in the Family Practice Center of the family medicine residency program of the Bowman Gray School of Medicine at North Carolina Baptist Hospital during the period from July 1, 1982 to December 31, 1982. These patients were seen both as scheduled appointments during regular clinic hours and after hours while on call. Four hundred and five patient encounters occurred while moonlighting during the same period: 119 patients were seen in the emergency departments of three small community hospitals near Winston-Salem; the remaining 286 moonlighting patients were seen in a "franchised" fee-for-service private family medicine practice in Winston-Salem. The clinical impressions at the time of the encounter were recorded for all patients seen in the Family Practice Center, whether during regular clinic hours or in after hours "emergency" clinic visits. Similarly, the clinical impressions, together with the age, sex and race of the patient, were recorded for all patient encounters while moonlighting.

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The clinical impressions were coded using the International Classification of Diseases, 9th revision (ICD-CM9).[5] The diagnoses of the patients seen in the Family Practice Center were coded by the North Carolina Baptist Hospital Medical Records department. The diagnoses of patients seen while moonlighting were coded by the authors. The diagnoses were grouped into the 18 major diagnostic categories of the ICD-CM9 to allow easier comparisons.

The data are presented in table 1. In several categories there are very marked differences in the percentages of patients seen while moonlighting compared with the residency-based outpatient experience. For example category 3 (which includes diabetes), category 5 (which includes depression and anxiety states), category 7 (which includes hypertension), category 11 (which includes normal pregnancy), and category 18 (which includes routine adult and well-child exams) were all more common in the Family Practice Center than in the moonlighting encounters. On the other hand category 8 (which includes upper respiratory infection) and category 17 (which includes lacerations and sprains) were much more common in the moonlighting encounters.

The differences in the patient populations seen in the Family Practice Center as opposed to moonlighting can perhaps be more easily seen in table 2 which lists the top 10 diagnoses ranked by frequency for the Family Practice Center and moonlighting data. Only acute upper respiratory infection and urinary tract infection appear on both lists.

Discussion

Moonlighting more than doubled the number of outpatient encounters in the six month period in question and provided significantly more exposure to urgent and emergency patient problems. This results in part from the fact that second year residents are only in the Family Practice Center an average of 10 half days per month and that few patients, a maximum of 10, were seen in any half-day clinic. The result is that a resident's schedule quickly fills with patients with chronic diseases, such as hypertension and diabetes mellitus, and with patients for routine care, such as health maintenance examinations and well baby check-ups, leaving little time for patients with urgent and emergency problems. The data demonstrate that moonlighting provides significantly more exposure to patients and to a wider range of patient problems than would normally be seen by second year residents at least in this particular family medicine residency program. In addition, moonlighting gives the resident significantly more experience in handling urgent and emergency medical problems.

Table 1
Number and Percent of Diagnoses by Diagnostic Category for Residency Based and Moonlighting Patient Encounters

Diagnostic Category	Residency Based Number	Residency Based Percent	Moonlighting Number	Moonlighting Percent
1. Infectious & parasitic diseases	25	7.9	23	5.0
2. Neoplasms	2	.6	2	0.4
3. Endocrine, nutritional & metabolic dis./immunity disorders	25	7.9	6	1.3
4. Dis. of blood and blood-forming organs	1	.3	1	0.2
5. Mental disorders	22	6.9	18	3.9
6. Dis. of nervous system & sense organs	10	3.2	39	8.6
7. Dis. of circulatory system	29	9.1	21	4.6
8. Dis. of respiratory system	47	14.8	102	22.4
9. Dis. of digestive system	6	1.9	16	3.5
10. Dis. of genito-urinary system	21	6.6	38	8.3
11. Pregnancy, childbirth & puerperium	21	6.6	2	0.4
12. Dis. of skin & subcutaneous tissue	9	2.8	22	4.8
13. Dis. of musculoskeletal & connective tissue	19	6.0	20	4.4
14. Congenital anomalies	—	—	1	0.2
15. Conditions originating in perinatal period	—	—	—	—
16. Symptoms, signs & ill-defined conditions	31	9.8	22	4.8
17. Accidents, injury, poisoning & violence	8	2.5	112	24.6
18. Supplementary classification (Preventive medicine, family planning, education, etc.)	41	12.9	11	2.4
	317	99.8	456	99.8

There is, of course, the very tangible benefit of extra income for residents who moonlight, but that is not relevant to this discussion. There is also an aspect of moonlighting that cannot be quantified, the feeling of being fully responsible for the patient. Nothing promotes more care with the history and physical examination and more thorough consideration of diagnostic and therapeutic options than that sense of total responsibility.

It appears that moonlighting is not a practice to be discouraged but one that should be encouraged as long as it does not interfere with the resident's performance in his residency program. Several steps could be undertaken to make moonlighting a better educational experience and to better safeguard patients seen by moonlighting residents. These entail better availability of the back-up doctors, follow-up on official interpretation of relevant studies such as x-rays and electrocardiograms, and timely chart review by the back-up attending or other physician with residents being made aware of any errors in diagnosis or treatment.

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Table 2
Top Ten Diagnoses Ranked by Frequency for Residency Based and Moonlighting Patient Encounters

Rank	Residency Based Number	Residency Based Percent	Rank	Moonlighting Number	Moonlighting Percent
1. Hypertension	21	6.8	1. Acute Upper Respiratory Infection	32	6.5
2. Diabetes Mellitus	19	6.2	2. Open Wound	28	5.7
3. Routine Medical Exam — Adult	18	5.9	3. Tonsillitis, Pharyngitis	29	6.4
4. Normal Pregnancy	13	4.2	4. Bronchitis	21	4.3
5. Depressive Disorder	11	3.6	5. Otitis Media	16	3.5
6. Acute Upper Respiratory Infection	10	3.3	6. Sprains	16	3.5
7. Anxiety State	9	2.9	7. Urinary Tract Infection	15	3.0
8. Urinary Tract Infection	8	2.6	8. Sinusitis	15	3.0
9. Routine Child Health Exam	8	2.6	9. Motor Vehicle Accident	14	2.8
10. Abdominal Pain	7	2.3	10. Tinnitus	9	1.8
		40.4			40.5

"Superdoc!"

THE North Carolina Medical Society's Midwinter Conference for 1984 — "Superdoc!" — took place at the Holiday Inn Four Seasons Convention Center in Greensboro on January 27. There were 250 attendees including physicians, Auxilians, office managers and other staff members from physicians' offices across the state. Three speakers addressed the conference on three separate aspects of managing a medical practice.

Mr. Robert C. Runde, President of RCR Associates in Charlotte, gave attendees a step-by-step guide to computerizing a physician's office, touching on advantages and disadvantages of owning your own computer versus time sharing on mini-, micro-, and mainframe computers. He discussed when to consider computerizing and which office tasks most lend themselves to computerization. Many of those in attendance had specific questions for Mr. Runde about software packages, computer systems, and interacting with third-party payors via computers. While responding to the questions, he readily acknowledged that not all medical offices need to be computerized, and he warned of various pitfalls for offices that are.

Dr. Joseph L. Price, a physician in family medicine in Philadelphia, addressed the conference on two subjects: computerized medical records as a tool for patient management, and continuing medical education in the next decade. Dr. Price, who has designed his own program for medical offices, spoke about how to use the computer to generate possible diagnoses for specific patient complaints, to check



Dr. Joseph L. Price



Mrs. Helen Boyette, an auxiliary member from Chinquapin, was among the attendees who raised questions for each of the three speakers.



Mr. Robert C. Runde



Mr. Leif C. Beck

for possible drug-drug or drug-food interactions, to flag abnormal results for further attention while discussing treatment with a patient or a patient with a consulting physician. He stressed the time-saving feature of streamlining patient management by using the computer in the office. Dr. Price also talked about applying modern technology to continuing medical education programs by using clinical simulation models on small computers or interactive video disk presentations.

Mr. Leif C. Beck, chairman of a medical consulting firm, offered attendees useful tips on personnel management, money management, and practice marketing. As both an attorney and a tax expert, Mr. Beck was able to talk knowledgeably about compensation policies in medical offices, when and why to pay into retirement accounts, how to calculate collection ratios. He ended the conference with a consideration of practice marketing and how important it is to physicians, not only in terms of public relations but also from the perspective of market analysis for a new single or multi-physician office.

The conference closed with a wine and cheese reception, co-sponsored by the NCMS and the Guilford County Medical Society.

EDITORIAL

A Curious, Interested Doctor at Peace with the Complexities of Biology

Eugene A. Stead, Jr., M.D.

I enjoyed reading Drew's account of the principles of drug monitoring.

Molecular change at the site of action of a drug is the final culmination of a series of distribution curves, each with a wide base. I remember the excitement when the purified glycosides of digitalis leaf became available. One distribution curve, namely the amount of active agent in each pill, was narrowed. Because of the differences in preparation of the pills, the amount of drug available for absorption varied widely. The distribution curves of bioavailability have a broad base and purification of the glycoside was of little help until the base of this curve was narrowed by better formulation by the pharmaceutical industry.

We then ran into a new set of distribution curves. The rate of disappearance from the blood and the degree of attachment of the active drug to cell membranes and cellular structures showed wide variability. The desired hemodynamic effects were not readily predicted by the serum levels. Drew states some of the reasons for this. Digitalis levels do allow us to identify our noncompliant patients and the patients who have a level that produces toxicity in the majority of patients. This is, of course, progress.

We know that a series of distribution curves determine the way the kidney excretes the drug. We know that the free level of the drug is altered by many other drugs. There must be at least 50 more distribution curves to be mastered before we can accurately define in quantitative terms the effects of digitalis.

Students of all types come to us to learn the science of clinical medicine. To me scientific medicine is a situation in which the doctor can control all the variables, elect a course and, after an absence of a number of days, return to find that the patient has stayed on the course charted by the doctor. Because of the complexity of biology with its thousands of overlapping distribution curves, this is rarely possible. I would rather have a doctor who continually observes the patient's course, knowing the depths of his ignorance, than a doctor who looks on himself as a scientist capable of controlling all the variables. An alert, curious, interested doctor who is at peace with the complexity of biology is a great asset to patients.

Kenneth Melmon,[1] a distinguished clinical pharmacologist, makes the same point in a paper entitled "Will the Sighted Physician See?"

"If we behave inappropriately we will continually press for miracle agents that do only good. Yet, in demanding substantial efficacy we are *asking* for chemical agents that intervene substantially in biological processes. Such agents used thoughtlessly or wrongly will produce disease. If we fail to think through this problem we will miss out on one of the biggest and most exciting challenges of medicine. That challenge is to observe the unexpected, to analyze it in the light of our knowledge and determine if we are truly seeing something new. It is the physician's privilege to observe biology in man, a model never fully replicated by laboratory animals."

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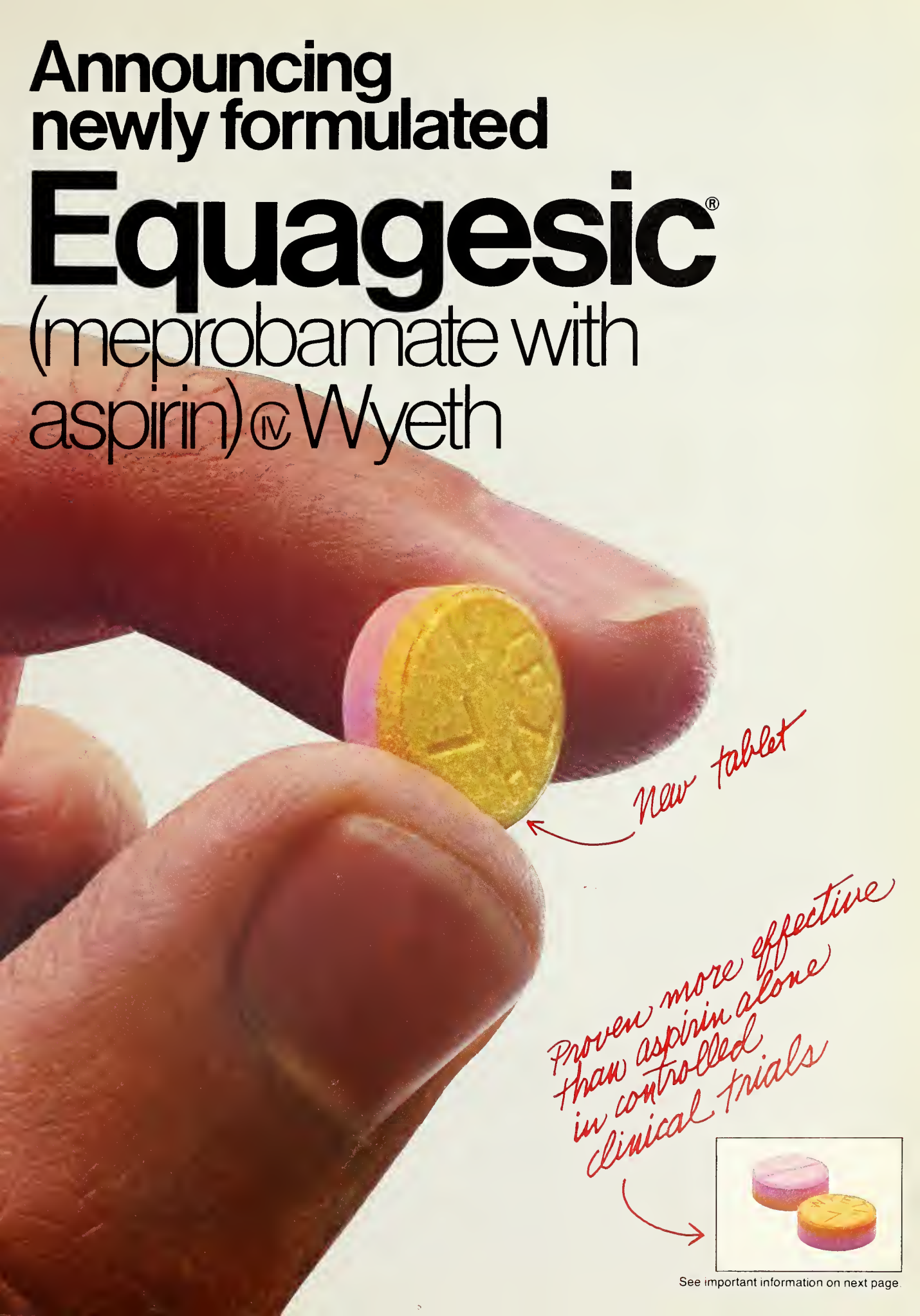
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ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria, allergic or idiosyncratic reactions to meprobamate or related compounds, e.g. carisoprodol, mebutamate, or carbromal.

WARNINGS:
ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE: DRUG DEPENDENCE
Physical and psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually, greater than recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms, e.g. anxiety, anorexia, or insomnia, or withdrawal reactions, e.g., vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinosis, and, rarely, convulsive seizures. Such seizures are more likely in persons with CNS damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation; symptoms usually cease within next 12- to 48-hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e.g., driving or operating machinery.

ADDITIVE EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION:
An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug.

Meprobamate passes the placental barrier. It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS:
ASPIRIN: Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney, to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS:
ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS: Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity.

GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate/mebutamate and meprobamate/carbromal. Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC"): Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms.

DOSAGE AND ADMINISTRATION:
Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSAGE:
Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdosage produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole-blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal. The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported. Acute simple overdose (meprobamate alone): Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS:
0.5-2.0 mg percent represents usual blood-level range of meprobamate after therapeutic doses. The level may occasionally be as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdosage, such as stupor or light coma.

10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment. Some fatalities occur.

At levels greater than 20 mg percent, more fatalities than survivals can be expected.

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol): Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated. Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption.

HOW SUPPLIED:
Scored tablets, bottles of 100, Redipak® strip pack 25's, Redipak® unit dose 100's, individually wrapped.

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Secondary Syphilis Masquerading as AIDS in a Young Gay Male

Raymond A. Smego, Jr., M.D., Randall W. Moreadith, Ph.D., Paul C. Kleist, M.D., and Donald L. Granger, M.D.

THIS is the story of our learning experience with a 38-year-old white male homosexual who was admitted to Duke University Medical Center with complaints of headache, fever, skin rash, and weight loss. His symptoms began six weeks earlier with the onset of vague low back pain and persistent temporal-occipital headaches that were partially relieved by salicylates. He also noted diffuse myalgias, generalized lymph gland enlargement, and night sweats which soaked his bedsheets. He had nausea and vomiting, anorexia, 3-5 non-bloody stools per day, and a 20-pound weight loss. Three discrete, non-pruritic erythematous macules had appeared over the ulnar eminence of his left palm and progressed over three weeks to become small papules with superficial scaling and crusting. There was no purulent discharge or bleeding from the lesions. Other lesions arose on the upper and lower extremities, abdomen, back, and face which were mildly tender to touch. The patient recorded intermittent temperatures to 102°F with rigors over this 6-week period.

At age 24 the patient had moved to New York City where he lived for 10 years. He admitted to having greater than 5,000 homosexual partners over the past 16 years, engaging in both active and passive anal-genital and oral-genital intercourse. He had been treated numerous times for gonorrhea. There was a history of oral and parenteral drug abuse in the distant past but none in the 10 years prior to admission. He moved to North Carolina in 1981 and claimed to have had an exclusive sexual relationship with a single male partner since that time.

There was an acniform rash on his face, neck, and trunk. There were several crusted, healing papular lesions on the left palm. Multiple erythematous macular and papular lesions, which appeared to be at different stages of development, were present on both lower extremities below the knees; several of these were slightly raised and had a distinct violaceous hue, and a similarly colored subungual lesion of the left great toe was present. There was generalized non-tender lymphadenopathy involving occipital, posterior and anterior cervical, supraclavicular, axillary, epitrochlear, and inguinal node groups. The liver was enlarged with a tender palpable edge; the spleen was not felt. Pertinent laboratory data included a WBC count of 5500/mm^3 with 54% polymorphonuclear cells, 35% lymphocytes, and 11% monocytes. The erythrocyte sedimentation rate was 52 mm/hr. A roentgenogram of the chest was normal. Lumbar puncture performed because of persistent headache revealed 2 lymphocytes/mm^3 with normal glucose and protein concentrations and a negative India ink exam. The serum VDRL was reactive at a dilution of 1:64; the cerebrospinal fluid VDRL was non-reactive. A serum fluorescent treponemal antibody-absorption (FTA-abs) test was positive. Serologic tests for *Toxoplasma gondii* showed an indirect hemagglutination titer of 1:64, and IgG and IgM antibody titers of less than 1:16 and 1:8, respectively. Hepatitis B surface antigen was negative but anti-HBs and anti-HBe antibodies were present; IgG antibodies to hepatitis A were also detectable. Serum protein electrophoresis showed hypoalbuminemia with a slight increase in gamma globulin concentration.

We felt that the patient was at a high risk for AIDS[1] and placed him on blood and enteric precautions. Biopsies of three geographically and morphologically distinct skin lesions revealed no evidence of Kaposi's sarcoma. They showed vasculitis with perivascular round cell infiltrates compatible with the histologic changes of secondary syphilis. Darkfield examination was attempted but no exudate could be expressed from multiple dry lesions. The patient was given benzathine penicillin G 1.2 million units intramuscularly in each buttock. Eight hours later he complained of slight nausea and developed a fever of 101.6°F which subsided spontaneously. Over the next 48 hours there was a significant decrease in the rash over his lower extremities and palm, and he was subjectively improved. He was discharged on the seventh hospital day. When contacted two months later, he reported a complete resolution of the skin lesions. He felt well and was gaining weight. He still had swollen lymph nodes in his neck but these were diminished in size since discharge.

Comment

The clinical features of secondary syphilis are protean, with constitutional, mucocutaneous, and parenchymal manifestations, and accordingly over the years the disease has been applauded as the "great imitator." A variety of morphologic skin lesions are the most commonly recognized physical findings, including macules, maculopapules, papulosquamous scales, pustules, and variations thereof. All stages may be present at one time and become widely distributed to the trunk and extremities. Location of lesions on the palms and soles strongly suggests the diagnosis. These lesions typically appear 2-10 weeks after the primary infection, last about 4-8 weeks and then resolve spontaneously. Constitutional symptoms such as malaise,

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anorexia, weight loss, arthralgias, and low-grade fever may occur in about 70% of cases. Highly infectious mucous patches, ulcers, and condyloma lata involving oral and genital mucus membranes, and painless generalized lymphadenopathy are also frequently seen. Less commonly, visceral involvement especially of the central nervous system can arise from seeding during spirochetemia.

In this gay male the combination of constitutional complaints, diffuse lymph node enlargement, and widespread skin lesions was mistakenly attributed to AIDS by both the patient and the medical staff upon admission. Indeed, many of these features were compatible with either the AIDS-related complex[1] which may represent a prodome to the development of full-blown AIDS, or with disseminated Kaposi's sarcoma.[1]

Histologic sections of multiple skin biopsy specimens revealed no evidence of Kaposi's sarcoma but demonstrated small-vessel vasculitis with perivascular mononuclear cell infiltration. These findings are consistent with the obliterative endarteritis produced by *T. pallidum*.

The diagnosis of secondary syphilis can be made serologically with demonstration of a reactive non-treponemal reaginic test such as the VDRL, plus a positive fluorescent treponemal antibody-absorption (FTA-abs) test. Quantitative VDRL titers greater than 1 : 16 indicate active, untreated infection. Darkfield examination of serous exudate from moist lesions of secondary syphilis with visualization of spirochetes will also establish the diagnosis. *T. pallidum* can at times be demonstrated from dry lesions and lymph nodes by saline aspiration.

A compatible clinical picture and serologic evidence of active infection strongly suggested a diagnosis of secondary syphilis in this patient. The therapeutic response to benzathine penicillin G, manifested by defervescence, an increase in the patient's sense of well-being, clearing of all skin lesions, and a reduction of lymph node size within one week further supported this impression. Such a response would have been inconsistent with a diagnosis of AIDS.

Secondary syphilis masqueraded as AIDS in this patient. When caring for sexually active gay males, common sexually transmissible diseases such as syphilis should be strongly considered and excluded. Serologic testing for *T. pallidum* should be performed on these patients, especially if skin lesions, adenopathy, and systemic complaints are present. Darkfield microscopy may further aid in diagnosis.

Reference

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Medical Memories — Tattoos: The Last Short Arm Inspection Conducted by the Army

John H. Felts, M.D.

A neurosurgical friend recently passed along a fascinating review of tattooing (Fried RI: The psychodynamics of tattooing: a review. Cleve Clin Q 1983;50:239-242), which recalled my own military adventures with the tattooed. One came during my internship more than three decades ago. The neurosurgical ward in those years at Walter Reed Army Hospital always had a few young paraplegic or quadriplegic patients, often paratroopers, whose spinal cord injuries had resulted not only from martial deeds but also from motorcycle accidents. We also had to care for a number of comatose young soldiers who had sustained head injuries in such accidents.

In my own personal diagnostic and prognostic classification, some patients were considered to have either motorcycle syndrome I or motorcycle syndrome II. Those with Type I had suffered spinal cord injury and were in varying stages of recovery and rehabilitation, while those in Group II were unconscious because of head injuries. Obviously, the prognosis was worse for those in the second category, although many quadriplegic patients also had rather dim prospects.

Almost all shared a few signs, partly attributable to their search for identity during the rite of adolescent passage, and partly to the catabolic stress of injury. They were tattooed, often elaborately, bearing such classical motifs as "Remember the Maine," patriotic phrases ("God, Country and Mother"), and phallic words and symbols — snakes, naked women who would wiggle when the deltoid was flexed, and the like. These decorative assertions of manhood were ironically negated by signs of negative nitrogen balance and feminization — gynecomastia, female pubic hair escutcheon, and soft testes. The very necessary acts of assertive masculinity, performed by gladiators on two-wheeled stallions as they flaunted their independence by shunning helmets, had led to their sexual neutralization with only tattoos left as dermal memorials.

Several years later, while serving in Europe with an infantry regiment, I again was faced with the need for considering the tattoo. Our division was scattered north of Frankfurt at posts along the Limes, the same line that marked the northern frontier of Caesar's legions when they had occupied Germany. The Romans had recognized that invasion from the east was most likely through the Fulda gap a few miles to the north and had deployed their forces accordingly. Our armies had, sensibly enough, been arrayed along the same line, again concerned about invasion from the east. The East German border was very near and our maneuvers were through parts of Hesse which soon became as familiar to us as they had to Caesar's legions. While I was there, archeologists, excavating within the walls of the caserne housing our 8th regiment in Butzbach, had unearthed artifacts of Caesar's 8th Nubian legion which had occupied the same site.

Away from home in a country recovering from a terrible war, it was hardly surprising to find venereal disease virtually epidemic. Despite their vigorous, well-coordinated efforts, American and West German venereal disease control personnel could do little but try to be sure that penicillin was appropriately dispensed. Catching the clap (also known as gleet, strain, rupture or running reins) under such circumstances may have been as symbolic of negotiating adolescence and defying authority as being tattooed.

My regimental commander at the time was authoritarian, something of a moralist, and given to deep thought. Well indoctrinated as to the importance of guarding the Fulda gap and extremely conscious of Russians just across the border, he concluded he must do more to protect our troops from spirochetes and gram negative cocci. Relying on sources unknown to the rest of us, he discovered that our potential enemies to the east were arranging for prostitutes to be infected and sending them in droves across the border on "sex patrols" to seek out "our boys," and lay them low with deadly germs. He further determined that "Pachucos," Hispanic delinquents in the Army, were somehow responsible for the passage of the infected from one Germany to the other and thus for the high VD rate among our troops. Something therefore had to be done to control the pox.

I was summoned to his office on a gray, cold, winter's day some 30 years ago and directed to devise measures to assure that members of our regiment would not be victims of such a plague. He also suggested that identification of Pachucos among us would help him to learn more about their operations in U.S. Army Europe. Trained only in how to seek out subversion of individuals by disease, I hardly knew how to think about the Colonel's revelations, much less approach them therapeutically and diagnostically.

Fortunately I remembered from earlier Army days as an

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enlisted man the payday parade known as Short Arm Inspection in which we marched in single file to qualify for our $21.00 a month. Wearing only our raincoats and boots, each of us before approaching the pay table faced an appreciative inspector, opened our raincoats and stripped our urethras. If no discharge was forthcoming, we were given our money and allowed to get dressed. Before going to town, however, we had to sign out and pocket a prophylactic containing mercury to combat Venus in the event we encountered her.

Pachucos identified themselves by a tattoo in the webbing between the thumb and index finger so that conspirators could be discovered at Short Arm if stripping were carried out twice, right-handed and left-handed, with the dorsum of the hand in front. Although by that time enlisted men no longer had to prove virtue every payday, the option to carry out an inspection as a health measure was retained, allowing us to inspect our troops for their own good when we thought it necessary. Each officer in our medical company was therefore assigned a corpsman and a battalion to inspect.

We roused our suspects in the early hours of the morning, described the proper procedure — raincoats, boots, single-file and manual techniques — and carried out our investigations. Several cases of urethritis were discovered, several men were AWOL and a few bearers of the terrible tattoo were found and reported to our Colonel. A few more turned out to have marked themselves with ink only, perhaps aspiring to participate in the nefarious doings of their role models. For them soap and water conferred innocence.

We never learned what happened to those truly tattooed, although our Colonel was certainly pleased when we reported our findings. Perhaps our data were ignored; at least the VD rate did not fall. Our Colonel might have felt that his efforts were insufficiently appreciated. At any rate, shortly after our pre-dawn reconnaissance, he completed his tour of duty and returned to the States.

His successor, more avuncular and less bedeviled, took a different approach. Rather than emphasize the problem, he instructed us not to report cases of gonorrhea, just to treat the infected. This order simplified my administrative life because we had to submit monthly venereal disease reports, in code lest our putative enemies learn of the sad medical and moral plight of our occupying army. My responsibilities included signing the report after it was encoded, but I had not yet been cleared by security to look at the coded report, which, of course, I could not decipher.

To cope with problems of morale our division had a Character Guidance Council with representatives from each detachment. We met monthly at division headquarters to derive the morality index for the past 30 days. This was done by plotting chapel attendance rate against VD rate. The council and the division commander were gratified at the improvement in morale and morality that the new commander had brought to our regiment. He and I were each proud to have contributed to such an achievement. I was also pleased that I may have directed the last nocturnal Short Arm Inspection in the history of the United States Army.

A Suggestion for Decreasing the Number of Medical Publications

DR. SKENE, in his characteristically able inaugural address at the last meeting of the American Gynecological Society, stated that during the past eight years, 804 books and 7505 journal articles and pamphlets had been added to the literature of gynecology. An inference may be drawn from this of the increase of medical literature in general. The question naturally arises whether this *embarras des richesses* is an unquestionable gain. It indicates, it is true, a wonderful diffusion of printed matter among a limited number of individuals, constituting one of "the learned professions," who, as a rule, lead exceptionally busy and useful lives. This being the case, they have a right to demand of those who purvey to their intellectual wants material which shall be digestible, assimilable, and calculated to insure healthy growth.

A survey leads us to the conclusion that the multiplication of journals has been entirely out of proportion to the demands of the profession, and that the majority of them, like too many of our younger institutions of learning in this country, are leading anything but a vigorous existence, their chief object being, apparently, to satisfy the ambition, of those concerned in their projection. Herein lies a grand indication for reform. Not that we desire to have *less* literature diffused, but *better*. This can be accomplished in several ways. One is concentration; the value of which is apparent enough, if one will but recall the most successful agencies around us for the advancement of knowledge, charity, or commerce. Another, is a more rigid censorship. With two hundred and more hungry editors, eager to grasp at anything which is offered, anything to fill their columns, no matter how immature, how unskillfully arranged, or how inconclusive, what wonder is it that complaints are constantly made of the valuelessness of a very large portion of the current medical literature? It is as ephemeral as the mist before the rising sun. Very aptly does Dr. Skene remark in the address to which allusion has been made, "this multitude of gentlemen, who write more than they read, 'scatter like deer at the sound of the hunter's horn' when compelled to defend themselves in public discussion before a tribunal of competent judges in well-regulated medical societies."

Another means by which the overproduction in medical literature may be checked, is by making the terms between author and publisher analogous to those which obtain in all ordinary business enterprises, a *quid pro quo*. The inducement held out by the majority of publishers to write for glory, with perhaps a score of reprints thrown in, is about as unfair and unreasonable, not to use a harsher term, as anything can be — to the author, if his contribution is worth spreading before the public; to the public, who pay their money to the publisher, if it is not worthy. The excuse that long established custom sanctions such a procedure, is an unworthy one. Custom sanctions many an abuse, which is nonetheless an abuse. It is noteworthy that there are a few high-minded publishers who do not follow this course, but pay liberally for all contributions as is the custom with THE MEDICAL NEWS. In general literature, those journals earn the largest profits which pay their contributors most handsomely. Why would not the same rule apply equally in medical literature? It would lead to the decrease of many current publications — no doubt to a process of consolidation among some of the survivors, to a merciless sifting of wheat from chaff, and to more care and painstaking on the part of authors. All of which would conduce to the general improvement of medical literature.

From *Medical News*, December 17, 1887, p. 717-718.

Options For Controlling Costs: A Survey of the American Public and Selected Professionals in the Health Care Field

Oh wad some power the giftie gie us
To see oursels as others see us!
It wad frae monie a blunder free us,
An' foolish notion.

ROBERT BURNS

LOUIS Harris and Associates, Inc. have played the role of God and let us see ourselves. The Equitable Healthcare Survey done by them for Equitable Life Assurance Society of the United States presents interesting contrasts between the views of doctors and those of a cross section of the public and of selected professionals in the health care field. Below are given the highlights of the survey.

1. There is a general consensus that fundamental changes are needed to make the U.S. health care system work better.

The American public, by a three-quarters majority, views the U.S. health care system as needing major changes. This view is shared by large majorities of employers, insurance executives, and unions, and by a marginal majority of hospital administrators. The one exception to this consensus lies with the medical profession: a clear majority of physicians who head medical societies believe that the health care system works pretty well and that only minor changes are needed to improve it.

2. The American public views both the cost of and access to health care services as areas in need of change.

Cost-related and access-related changes head the list of changes in the health care system considered most important by the American public and union leaders. The other professional groups acknowledge the need for cost-related changes, but they also emphasize public education regarding medical programs and costs. The primary change sought by physician leaders is less government interference and regulation.

The public's concern about access centers around care for the elderly. Based on their personal experiences, however, the American people, including the elderly, are largely satisfied with the quality of and access to health care services, and with health insurance benefits.

From Equitable Life Assurance Society of the United States, 1285 Avenue of the Americas, New York, NY 10019.

3. Barriers to medical care.

The 14% of the American public who did not obtain needed medical care in the twelve months preceding this survey include sizable numbers of the uninsured (32%) and the unemployed (28%). The primary barrier to obtaining needed medical care is the cost of this care.

4. There is widespread dissatisfaction with the cost of hospitalization.

While a slight majority of the American public are dissatisfied with the total cost of health care as well as out-of-pocket costs, their criticisms are focused mainly on the cost of hospitalization and the cost of laboratory work and X-rays done outside hospitals and clinics. Smaller majorities of the public also consider the cost of doctors' visits and prescription drugs to be unreasonable.

The view that hospital costs are unreasonable is shared by an overwhelming majority of union leaders, corporate benefits officers, and insurance executives, and by a significant majority of physician leaders. Even among hospital administrators, 40% view hospital costs as unreasonable.

5. There is very little consensus on the main cause of increased spending on health care.

The debate about the main underlying cause of the escalation of health care spending is still unresolved. While slightly more than 40% of the American people view this escalation as due to "the increasing cost of the same services," one-third of this group blame "the use of new and more expensive treatments and equipment." Physician leaders and hospital administrators view the latter reason as the primary cause of escalating expenditures.

"People using more services than they used to" is not acknowledged as a major cause of escalating expenditures by the American public. However, about 30% of physician leaders and hospital administrators recognize it as a primary cause of this escalation.

The views of corporate benefits officers and union leaders tend to parallel those of the public.

6. The health care system as it is today does little to encourage price competition.

Only 16% of the American public have selected a doctor because of lower fees. Comparison shopping for prescription drugs is viewed as easier than shopping for health insurance, doctors, or hospitals. Shopping for laboratory

tests and X-rays is viewed as difficult by a sizable majority of the American public.

7. The lack of price competition in the system is acknowledged as a reason for the rise in health care spending.

Large majorities of the American public and of all of the professional groups *except* the physician leaders agree that "the lack of competitive pricing among doctors, hospitals, or nursing homes" contributes to the rise in health care spending.

The opinions of physician leaders contrast sharply with those of all of the other groups, including hospital administrators. While only 37% of the physician leaders blame "lack of price competition" for the increase in health care spending, 68% of hospital administrators do so.

On the other hand, there is general consensus that as long as third-party payers assume all or most of the cost of health care, there is no incentive for patients or providers to cut spending or costs.

8. The American people and most professionals recognize that programs and practices that benefit them are also a source of inflation in health care spending.

Majorities in all groups mention the following as contributing to cost escalation: the increased availability of employer-paid health insurance, hospitalization for minor ailments, the growth of malpractice suits, people staying in hospitals longer than is necessary, the aging of the population, increased availability of government funded programs, and overuse of tests by doctors.

Physician leaders, in general, are least willing to recognize the actions of their own profession as contributing to the rise in health care spending, while hospital administrators have a more balanced view. While majorities of respondents in all groups recognize that "one of the problems in health care is that there is no real competition to keep prices down," only 27% of the physician leaders agree with this view.

9. The American public is ready to accept a broad range of cost-containment proposals.

The conventional wisdom that the American public will resist major changes in the health care system is called into question by the findings of this study.

The American public is remarkably willing to accept a broad range of cost-containment policies, including those that would increase out-of-pocket costs to the public and minimally curtail freedom of choice among health care options.

This willingness to accept proposed changes is based on the belief that the changes will be effective in slowing health care cost inflation. These findings suggest that the public would be willing to accept such changes because of a sense of realism and an understanding that the changes are necessary, rather than because they support them enthusiastically.

The proposals that the public considers most acceptable are: alternatives to the use of hospitals for minor surgery, tests, or the treatment of the chronically ill, increased cost-sharing in the payment of health insurance premiums and increased deductibles, diagnosis-related cost caps on hospital and doctors' fees, requiring second opinions on non-emergency surgery, insurance rate incentives for preventive care, prepaid plans and preferred provider plans, and using low-cost alternatives to physicians and hospital care.

10. Professional groups have varying perspectives on the cost-containment proposals.

Union leaders, corporate benefits officers, and insurance executives generally share the views of the American public, and they are willing to accept almost all of the proposed changes in the health care system.

Hospital administrators are generally willing to accept changes in the health care system in the interest of cost containment, even if the changes mean a reduction in hospital use or a restriction on the fees charged by hospitals.

Physician leaders are the least willing of all groups surveyed to accept — or even to recognize as effective — changes that are likely to adversely affect the financial incentives for their profession.

11. Most corporate executives whose companies have implemented new cost-containment programs believe that the programs are effective.

Corporate executives whose organizations have had experience with various cost-containment measures are more likely to judge them as effective than are those who have had no experience with these measures. This is particularly true for programs that require increased cost-sharing by employees and for those that provide better coverage for lower cost health care options, such as home care for the chronically ill and the use of nurse practitioners, midwives, and physicians' assistants.

12. There is widespread opposition to a proposed tax on employer-paid premiums.

One policy that is rejected by the majority of respondents in most groups as ineffective and unacceptable as a cost-containment measure is the often-discussed individual tax on a portion of the employer-paid health insurance premiums. The physician leaders are the only group in which a clear majority find this proposal to be both effective and acceptable.

13. Shifting costs from Medicare patients to other patients is viewed with disfavor.

The majority of the American public and majorities of all of the professional groups disapprove of the practice of shifting costs from Medicare patients to other patients. This disapproval is voiced as strongly by those who do receive Medicare benefits as those who do not.

14. There is general support for programs that provide health insurance for the unemployed, but it diminishes sharply when viewed as resulting in greater costs for other people.

The American people (including the unemployed) and corporate benefits officers reveal a marginal reluctance to support health care benefits for the unemployed if such

benefits result in higher direct or indirect costs to other people. However, sizable minorities (of more than 40%) are in favor of these benefits despite their costs.

Physician leaders, insurance executives, and hospital administrators, on the other hand, favor providing these benefits.

15. Overall, the American public reveals awareness of and concern about health care issues.

The majority of the American public are remarkably aware of and concerned about problems related to health care coverage and health care services. This is reflected in the relatively insignificant numbers of respondents who give "not sure" or "no opinion" responses to the questions asked in this survey.

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J-4044 January 1984



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If you still believe in me, save me.

For nearly a hundred years, the Statue of Liberty has been America's most powerful symbol of freedom and hope. Today the corrosive action of almost a century of weather and salt air has eaten away at the iron framework; etched holes in the copper exterior.

On Ellis Island, where the ancestors of nearly half of all Americans first stepped onto American soil, the Immigration Center is now a hollow ruin.

Inspiring plans have been developed to restore the Statue and to create on Ellis Island a permanent museum celebrating the ethnic diversity of this country of immigrants. But unless restoration is begun now, these two landmarks in our nation's heritage could be closed at the very time America is celebrating their hundredth anniversaries. The 230 million dollars needed to carry out the work is needed now.

All of the money must come from private donations; the federal government is not raising the funds. This is consistent with the Statue's origins. The French people paid for its creation themselves. And America's businesses spearheaded the public contributions that were needed for its construction and for the pedestal.

The torch of liberty is everyone's to cherish. Could we hold up our heads as Americans if we allowed the time to come when she can no longer hold up hers?

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You are invited to learn more about the advantages of corporate sponsorship during the nationwide promotions surrounding the restoration project. Write on your letterhead to: The Statue of Liberty-Ellis Island Foundation, Inc., 101 Park Ave, N.Y., N.Y. 10178.



KEEP THE TORCH LIT

Save these monuments. Send your personal tax deductible donation to: P.O. Box 1986, New York, N.Y. 10018. **The Statue of Liberty-Ellis Island Foundation, Inc.**

STATUE OF LIBERTY—ELLIS ISLAND CENTENNIAL CAMPAIGN
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BP-SPEC 1983

A Note of Caution From New Bern:

Computer Diagnoses

Devereux H. Lippitt, M.D.

WHAT about these interpretive computer programs that juggle laboratory data and come up with a list of diagnoses or interpretations? They have been around for years but lately there is a push by laboratory suppliers to sell the hardware and programs together in a single package. Computers have had their greatest use in adding qualifying comments on a single unusual test when the result is out of range. In fact, in a community hospital most of the rarely done tests will be sent to central commercial laboratories, and cautions concerning false positives, interfering drugs, and so forth are added to the reports. The computer has merely located the comment and printed it, much like an aide could do with a rubber stamp.

Greater complexity is involved when a combination of tests is used to arrive at an interpretive comment or diagnosis. The decision tree or algorithm is the ultimate in formal logic but few problems can be solved in this way since so many consecutive yes/no answers are required. Instead, by rapid but obscure mathematical manipulations such as multivariate data analysis a computer may reach a decision based on many items of quantitative data. The weather is predicted with greater than human accuracy by this method. In medicine, risk factors can be calculated and the percentage risk for a given diagnosis given. This may help an inexperienced physician or a paramedic estimate the need for surgery or a CAT scan. If the risk were too low, perhaps the intermediary would have a rule not to pay.

Some of the older sorting methods for diagnosis from SMA 12 reports were based on punch cards and could yield a variety of diagnoses sometimes more humorous than valuable. Such methods never enjoyed sustained popularity. When a pattern of numbers or multivariate analysis is used for interpretation rather than individually significant data, management based on this might have a medieval aura. This recalls Montaigne's aphorism: "It is more of a job to interpret the interpretations than the things, and there are more books about books than any other subject." The instantaneous elimination or tolerance of absurd possibilities might itself require much judgment and knowledge.

The method of the mind in diagnosis differs entirely from the computer. We leap to answers often based on equivocal data simply by intuition. Sometimes illogical ideas or dimly remembered similarities can lead to a solution. How to program computers to use such heuristic methods of thinking which are quite efficient and effective continues to occupy and baffle mathematicians.

When we recall that 85-90% of diagnoses on clinically ill patients are made from the history and physical, the possibilities left for the computer to shine are largely interpretive rather than diagnostic. It's going to be interesting to see if the laboratory supply houses can sell these programs these next few years.

From Craven County Hospital Corporation, P.O. Box 2157, New Bern 28560.

First in a series of reports from your colleagues about Medical Mutual Insurance Co. of North Carolina

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IN STATE

April 25

"Current Concepts in Otolaryngology for the Primary Physician"
Place: UNC
Fee: $50
Credit: 6½ Hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

April 28

Alzheimer's Disease Update
Place: UNC
Fee: $15
Credit: 5 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 10-11

Infectious Disease Update 1984
Place: Greensboro
Fee: $75
Credit: 11 hours Category I AMA
Info: Fred Levick, Greensboro AHEC, 1200 North Elm Street, Greensboro 27401. 919/379-4025

May 10-12

North Carolina Chapter of the American College of Surgeons
Place: Boone
Info: Richard W. Furman, M.D., 702 State Farm Road, Boone 28607. 704/264-2340

May 16

Progress on Type 2 Diabetes
Place: Raleigh
Fee: None
Credit: 3 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 17-18

Social Behavior in Autism
Place: Chapel Hill
Fee: $25 in-state; $100 out-of-state
Credit: 12 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 17-19

Floyd W. Denny Alumni Lecture Series
Place: Chapel Hill
Info: Gerald W. Fernald, M.D., Pediatrics, 509 Burnett-Womack Bldg. 229H, UNC School of Medicine, Chapel Hill 27514. 919/966-2085

May 18-20

Pathokinesiology of Cerebral Palsy
Place: Chapel Hill
Info: Darlene S. Slaton, Physical Therapy, C 221H, UNC School of Medicine, Chapel Hill 27514. 919/966-4708

May 25-26

13th Annual Seminar: Gut and Lung Problems in Pediatrics
Place: Durham
Credit: 12 hours
Fee: $60
Info: Alexander Spock, M.D., Box 2994 Duke University Medical Center, Durham 27710. 919/681-3364

May 25

Pediatrics Day
Place: Greenville
Credit: 7 hours
Fee: $55
Info: Mary C. Valand, Box 7224 ECU School of Medicine, Greenville 27834. 919/758-5200

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine
Place: Sea Level
Info: M. Valand, ECU School of Medicine, PO Box 7224, Greenville 27834. 919/758-5200, ext 208

May 31-June 2

Approaches to Ethical Decision Making
Place: Durham
Info: Nettie Wilburn, UNC-CH School of Nursing, Carrington Hall 214H, Chapel Hill 27514. 919/966-3638

June 1-2

Neurology for the Primary Physician
Place: Chapel Hill
Fee: $100
Credit: 11 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118.

June 5

Duke Tuesday
Place: Durham
Credit: 5 hours
Info: L. Mace, Urology, Duke U Med Center, Box 3707, Durham 27710. 919/684-2033

June 6-7

Fellows Symposium
Place: Chapel Hill
Info: John J. Frey, M.D., 231 MacNider Bldg 202H, Chapel Hill 27514.

June 17-22

Health Promotion — Wellness Institute
Place: Raleigh
Fee: $250
Credit: 30 hours
Info: NC Health Promotion, Wake AHEC, 3000 New Bern Ave, Raleigh 27610. 919/755-8018

June 22-23

North Carolina Affiliate, American Heart Association, 35th Annual Meeting and Scientific Sessions
Place: Durham
Info: N.C. Heart Association, Chapel Hill 27514

July 9-14

26th Annual Postgraduate Course/Morehead Symposium
Place: Atlantic Beach
Credit: 25 hours
Info: C. Easterling, Duke U Medical Center, Box 3306, Durham 27710. 919/684-6485

OUT OF STATE

April 9-11

"Gold Coast Seminar: OB/GYN"
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

May 7-9

Gold Coast Seminar: Medicine
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306 Duke University Medical Center, Durham 27710. 919/684-6485

May 10-12

Current Concepts of Clinical Infectious Diseases

Place: Hot Springs, VA
Fee: $220, $165, $295
Credit: 13¾
Info: Gerald L. Mandell, M.D., Univ of Virginia, Charlottesville

May 18-19

Practical Dermatology for the Non-Dermatologist
Place: Williamsburg, VA
Fee: $90
Credit: 7 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 24-27

8th Annual Radiology Symposium
Place: Hilton Head, SC
Fee: $350
Credit: 19 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 30-June 2

AACA 1984 Spring Seminar in Anesthesiology
Place: Hilton Head, SC
Info: Amer Academy of Clinical Anesthesiologists, P.O. Box 11691, Knoxville, TN 37939-1681. 615/588-6279

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine
Place: Sea Level, GA
Info: Mary C. Valand, CME, ECU School of Medicine, Greenville 27834. 919/758-5200

June 4-8

Cornell University Diagnostic Radiology Update Emphasizing Advances in Imaging and Interventional Procedures
Place: Bermuda
Credit: 100 hours
Fee: $400, $300
Info: Ann Wold, Gallagher/Wold, Inc., 420 Lexington Ave., New York 10170. 212/986-1277.

June 27-30

Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Credit: 15.5 hours Category 1 AMA
Fee: $350
Info: Dermatology, Box 2987 Duke University Medical Center, Durham 27710. 919/684-6728

July 2-7

Midsummer Family Practice Digest
Place: Myrtle Beach, SC
Credit: 30 hours
Info: NCAFP. 919/781-6476

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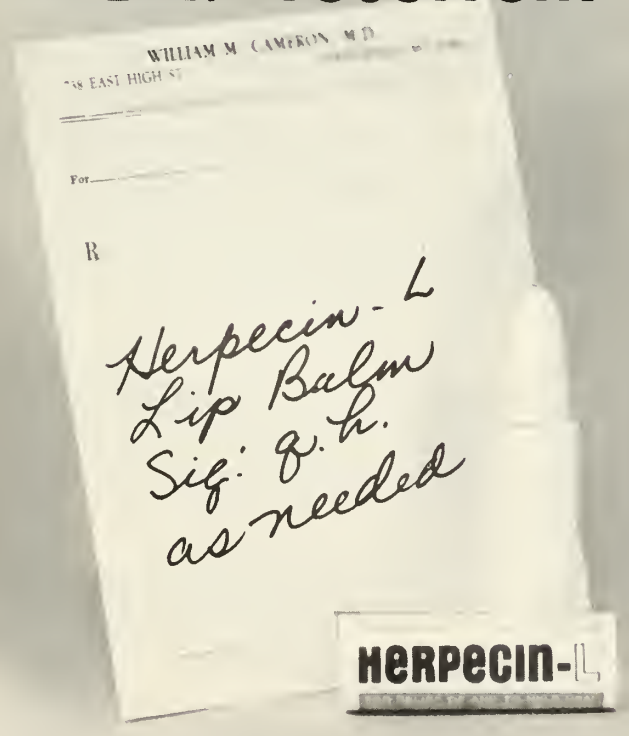
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WILLIAM LESTER ADCOCK, JR., M.D.

Dr. Adcock, who died on August 26, 1983 arrived in Raleigh to practice neurosurgery nineteen years ago. He came well-educated, holding gold keys as evidence of his successes in scholarship at the college and medical school levels, and well-trained in his specialty. Dr. Adcock served as President of the Wake County Medical Center staff in 1980.

Dr. Adcock, the oldest of five children, grew up in Rockingham, N.C., admiring a highly respected local physician, whose career served as a model. For college admission Dr. Adcock applied only to the then Wake Forest College, the only university he wished to attend. Recognizing his intellect, they took him. Subsequently he attended the Bowman Gray School of Medicine. Dr. Adcock served as a Captain, U.S. Army, 1957-1959, assigned to the 2nd General Hospital, Landstuhl, Germany, providing neurosurgical support for the U.S. Army ground forces in Europe and the Sixth Fleet in the Mediterranean.

Dr. Adcock had a wide variety of interests and hobbies: collecting classical music records, coins, stamps, and army vehicles. He was a great connoisseur of wine, food and flowers. Roses were his special favorite. A much admired rose garden is planted beside his office and he often wore a rose in his lapel.

While eminently memorable as a practitioner, it was as a person that he was most unforgettable. He was a classic example of a man whose gruff manner served as a facade to cover a gentle nature and a generous heart. On at least one occasion he purchased a hospital bed for home use by one of his pediatric patients. His devotion to his family was intense. He spoke often of the joy of his marriage to Naomi and his pleasure in his relationships with his three children, Catherine Ellen, a dental hygienist; Dorothy Elizabeth, a second year medical student at her Dad's alma mater; and Jeffrey David, now in his sophomore year in Computer Science at Chapel Hill.

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Letters to the Editor

Mediation Committee Reports on Complaints

To the Editor:

The North Carolina Medical Society Mediation Committee continues to have numerous complaints from patients regarding records of physicians. The following is a statement from the AMA Judicial Council Current Opinion regarding availability of information.

"The AMA believes the interest of the patient is paramount in the practice of medicine, and everything that can reasonably and lawfully be done to serve that interest must be done by all physicians who have served or are serving the patient. A physician who formerly treated a patient should not refuse for any reason to make his records of that patient promptly available on request from another physician presently treating the patient. Proper authorization for the use of records must be granted by the patient. Medical records should not be withheld because of an unpaid bill for medical services.

"According to the AMA, notes made in treating a patient are primarily for the physician's own use and constitute his personal property. However, on request of the patient a physician should provide a copy or a summary of the record to the patient or to another physician, an attorney or other person designated by the patient. Several states have enacted statutes that authorize patient access to medical records. These statutes vary in scope and mechanism for permitting patients to review or copy medical records. Access to mental health records, particularly, may be limited by statute or regulation. A physician should become familiar with the applicable laws, rules or regulations on patient access to medical records. The record is a confidential document involving the physician-patient relationship and should not be communicated to a third party without the patient's prior written consent, unless required by law or to protect the welfare of the individual or the community. Medical reports should not be withheld because of an unpaid bill for medical services. Simplified, routine insurance reimbursement forms should be prepared without charge, but a charge for more complex, complicated reports may be made in conformity with local custom."

The Mediation Committee also receives complaints from members of the family regarding information concerning illness of a loved one. We feel that more communication between the physician and family members during serious illness and especially in the death of a patient would alleviate many of these complaints. More detailed information to members of the family especially in critical illnesses or death of the patient would show sincere consideration and compassion by the physician and would certainly be most appreciated by the family.

D. E. Ward, Jr., M.D., Chairman
Mediation Committee, NCMS
2604 North Elm Street
Lumberton 28358

Davison Stories Keep Coming

To the Editor:

Dr. Davison was made a Master of the American College of Physicians and was the only pediatrician to receive this honor. The meeting was in Chicago and we went out together.

On the trip we were talking about Dave's trip to England at the end of World War II in Europe. Dave was one of a group of VIPs waiting in Washington, D.C. to get a government flight to London. He was on his way to visit the Duke Unit, the 65th General Hospital stationed at Redgrave Park in Suffolk, in support of the 8th Air Force.

A few hours before the flight to London, VE Day occurred and all the military brass on the flight cancelled out. Dave found himself taking off on a huge Army transport to London as the only passenger. About four hours into the flight over the Atlantic he decided to go to the flight area and speak to the crew for a chat. Much to his amazement, there was no one in the pilots' area. The plane was on automatic pilot and the crew was below for coffee.

When I went to pick him up in a jeep at ETO headquarters in London to take him out to the 65th General Hospital, he was still recovering from his unique trip.

Joseph B. Stevens, M.D.
1017 Professional Village
Greensboro

Some Problems Have Solutions

To the Editor:

For many years, organized medicine has been on the defensive, fighting one brush fire or another.

May I suggest that now is an excellent time for us to become positive and provide some leadership for the nation.

I. PROBLEM

Medicine is now being criticized and partially rightly so for the cost of medical care. There are many facets to this problem.

1. Medicine in 1984 is expensive because America is receiving some of the best medical care in the world — that's good.
2. Medicine in 1984 is expensive because we are practicing defensive medicine.
   a. Malpractice premiums are up because there are more and larger suits. These premiums ultimately come from the patient.
   b. We do more lab studies and hospital procedures than necessary as a defense against malpractice problems. This expense ultimately comes from the patient.

Throw your brain out of gear for a few moments and let's see how we can attack this part of the problem. I do not

propose to have all the answers, but let's toy with a few ideas.

II. SOLUTION

Let's let organized medicine, the North Carolina Medical Society, the North Carolina Hospital Association, medical insurance companies, etc., pool our brain power and take the lead in a solution to help medicine and to help the patient. Let's cut some of these costs.

Let's try the following for a starter:

1. Let's jointly ask the Legislature to make arbitration a fact in North Carolina.
2. Let's get the insurance companies to offer medical insurance to large companies and individuals so that the co-insurance required from the patient is less if the recipient signs a waiver stating that he is willing to abide by arbitration if a dispute arises.
3. Let the M.D. have a guaranteed reduction in malpractice premiums if he signs a waiver stating that he is willing to abide by arbitration if a dispute arises.

If the patient, the insurance companies, we the people, and the M.D.'s all win, then it is a good game.

Bruce B. Blackmon, M.D.
Fifth District Councilor
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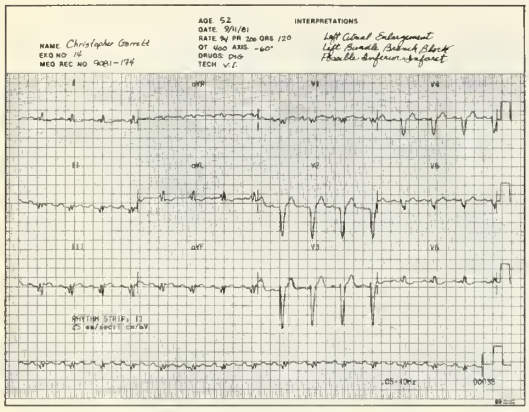
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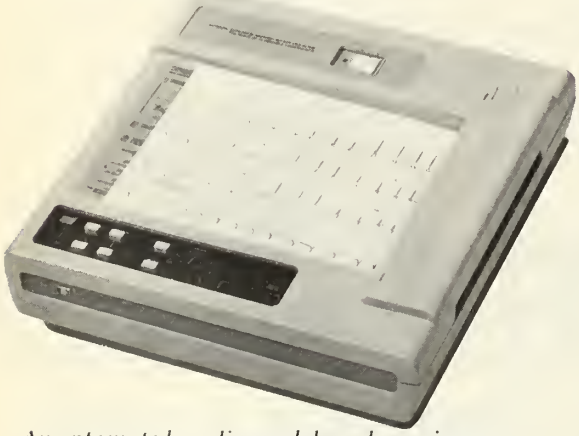
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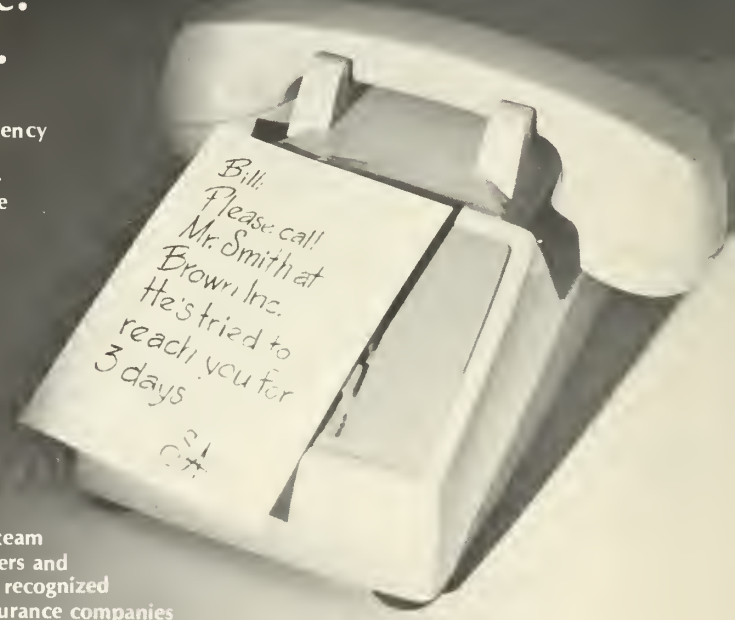
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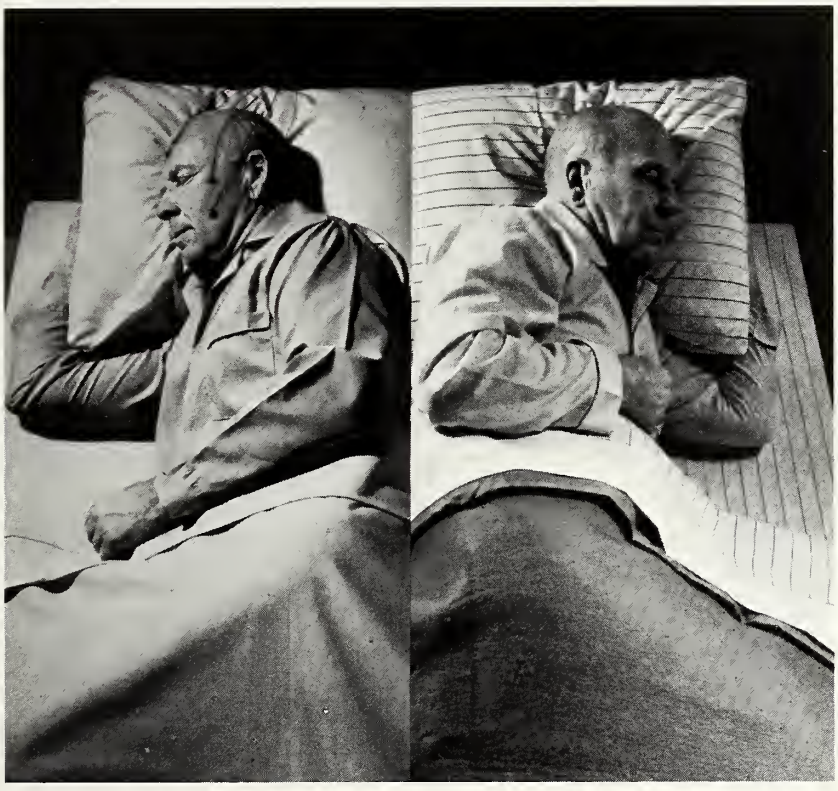


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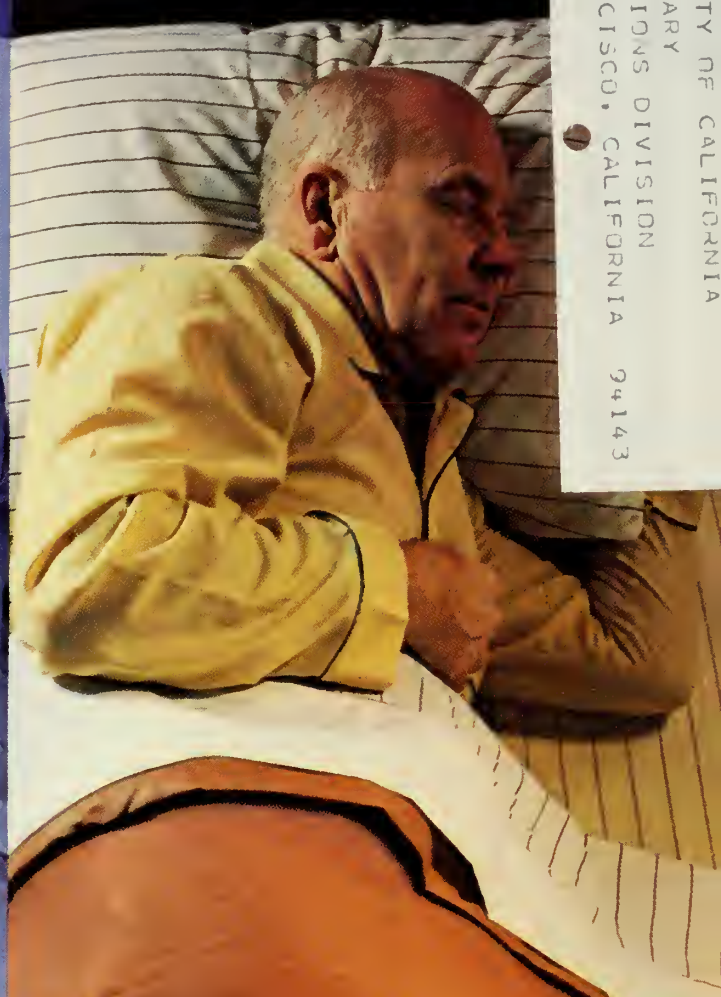
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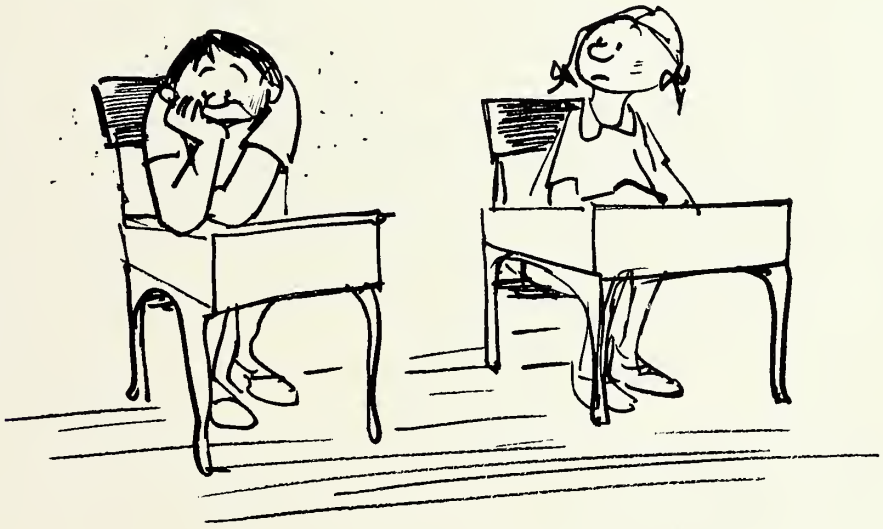
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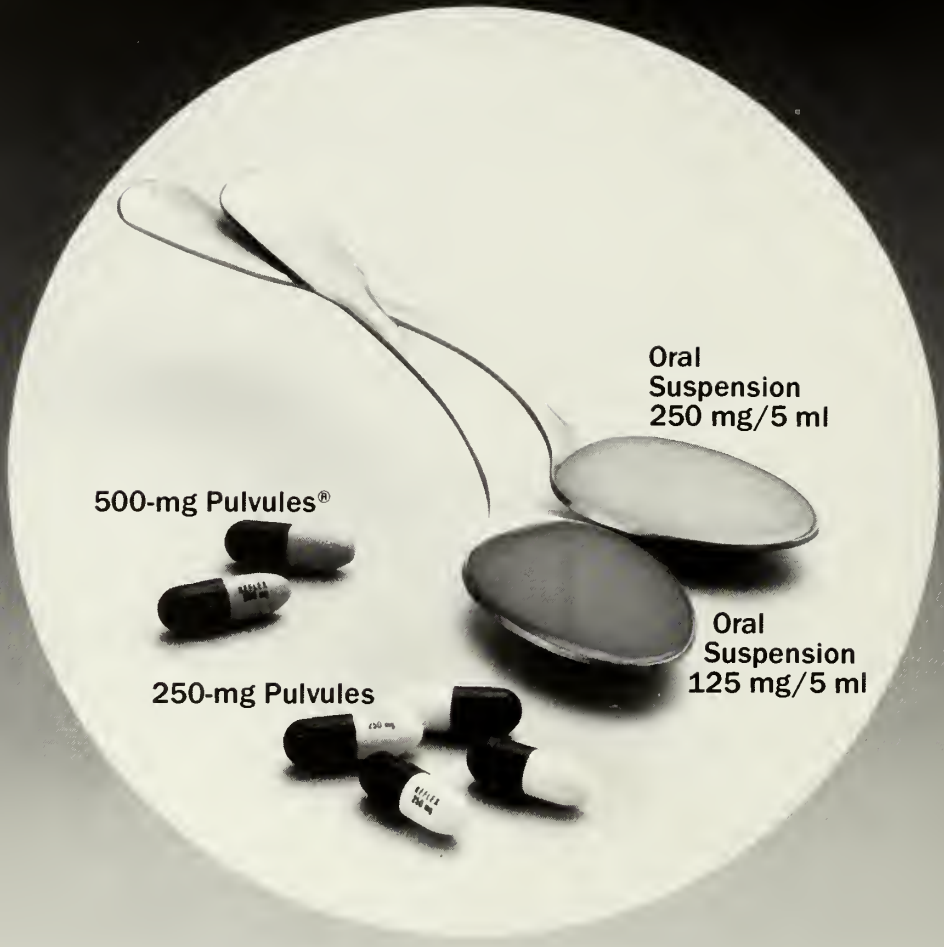
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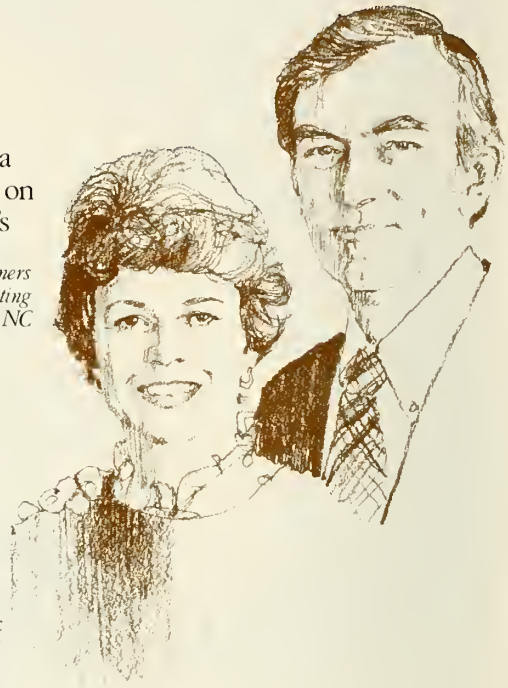
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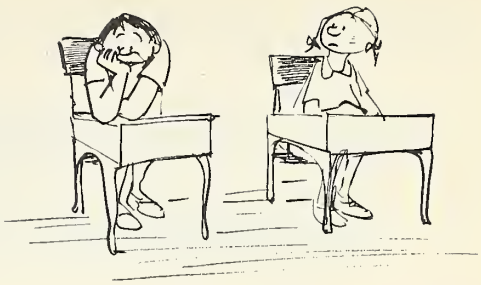
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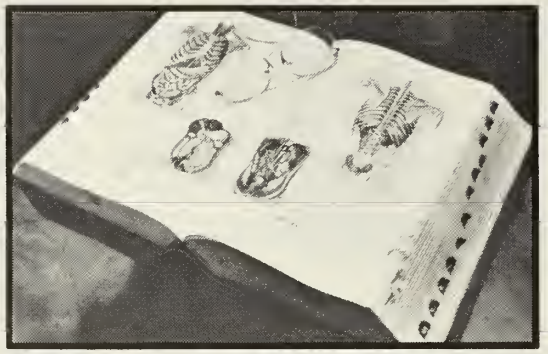
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SCIENTIFIC ARTICLE

To Comfort Always: Strategies for Pain Management in Terminal Cancer

Linda M. Frazier, M.D. and Errol J. Kohl, R.N., B.S.N.

"To cure sometimes, To relieve often, To comfort always."
Fifteenth century folk saying on the duties of a physician.

OPIUM has been used since Babylonian times and injectable morphine has been available since before the Civil War. Despite this prolonged opportunity to learn how to use narcotic analgesics, physicians often use them poorly in managing pain.[1] This is in part because pain has many faces: strategies that work well for the acute self-limited pain of renal colic or trauma are neither appropriate nor effective for chronic low back pain or porphyria. The pain of cancer in its early stages can be managed like pain from other causes, but when the cancer becomes advanced pain becomes more complex and additional strategies are needed. The following case illustrates strategies for managing severe pain in terminal cancer.

A patient with advanced cancer presented with abdominal pain.

Case: *A thirty-one-year-old man developed progressive abdominal pain and weight loss. At a local hospital he was found to have gastric adenocarcinoma with metastases to the posterior abdominal wall and para-aortic lymph nodes. He received radiotherapy and 5-fluorouracil but deteriorated over the next seven months and was referred for evaluation of severe abdominal pain, wasting and ascites. His only medication was Demerol, 100 mg intramuscularly (IM), every four hours.*

A team of two physicians began caring for him. Physical examination revealed an alert, oriented, cachectic man in moderate distress from abdominal pain. Blood pressure was 130/110 mm Hg and respirations were 22 per minute. There was dullness at both lung bases. The abdomen was tender and tensely distended with shifting dullness and prominent venous collaterals; pitting edema extended to the knees; axillary and inguinal lymph nodes were enlarged. Hemoglobin was 8.2 mg/dl (normal 12-17), creatinine was 2.1 mg/dl (normal 0.6-1.6), and albumin was 3.1 g/dl (normal 3.9-5.4).

The physicians made plans to evaluate his tumor.

In their initial assessment, his physicians commented on the rarity of gastric cancer in a thirty-one-year-old and they speculated at length about the cause of his ascites. They felt the patient was "preterminal" and wanted to make him comfortable, but they asked four consultants to recommend further cancer treatment. They considered performing an abdominal paracentesis, lymph node biopsy, renal sonogram and a creatinine clearance. They thought about beginning iron therapy, about improving his nutrition and about helping him spend time with his family. Instead, they ordered serum transaminases, a hepatitis B surface antigen, VDRL, and an abdominal x-ray. They prescribed milk of magnesia, Colace and Tylox, two capsules by mouth every six hours as needed for pain.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

Comment: The doctors caring for this unfortunate patient correctly concluded that he did not have long to live because the prognosis of unresectable gastric cancer is poor and because physical exam showed that the tumor was widespread. They also decided appropriately to make him comfortable. But they found it difficult to achieve this goal. They would have been able to make this patient more comfortable by using several basic pain control strategies, which we discuss below.

The physicians did not make a pain assessment.

It is remarkable that the primary physician duly recorded "abdominal pain" as the patient's chief complaint, but then failed to mention it in his three-page case assessment. Although he wanted to make the patient comfortable, he did not plan explicitly to do so. His associate made a twelve-item problem list, but did not include abdominal pain as one of the problems. Both physicians thought about the cancer and tests that could measure its spread, but they overlooked the patient's significant pain. They made explicit plans to evaluate and treat every aspect of his disease except pain.

They did not make a pain management plan.

In contrast, a consulting internist considered pain control the most important objective, and the nurse's major plan was to administer pain medications promptly at the patient's request. Nevertheless, the first analgesic order was haphazard, reflecting the fact that the doctors had made no pain assessment or pain management plan at the outset: For this patient with severe pain caused by advanced cancer, they prescribed Tylox, two capsules by mouth every six hours as needed. This is much less analgesia than the Demerol given at the other hospital. Furthermore, the Tylox was ordered only "as needed for pain," and not on a regular basis.

Pain Management Strategies

1. Make a pain assessment.

Pain control may be the only thing the physician can do for a terminal cancer patient, but this goal must be identified before it can be achieved. A successful pain management strategy depends on an accurate baseline pain assessment and frequent follow-up assessments. The pain assessment may be difficult because patients express themselves in different ways. Many patients feel that their pain is typical of their disease and that doctors and nurses must already know how much pain they are experiencing; they may feel that if pain medication were necessary the doctor or nurse would surely give it. Other patients stoically wait until their pain is unbearable before they mention it. This can lead to poor pain management when the doctor or nurse believes that patients will always request pain medication if they are in pain. Doctors and nurses should ask themselves whether any other attitudes are influencing their pain assessment. Do we assume that patients with the same disease should have the same amount of pain? Do we doubt patients who express their pain in a culturally unacceptable manner? Do we doubt patients who complain of severe pain but lack "signs" of pain such as tachycardia, diaphoresis, grimacing or protective movements? These sympathetic physiologic responses that are so often present in acute pain may be absent or less pronounced in chronic pain because the patient is unable to maintain a constant state of "fight or flight."

We may also assume incorrectly that a cancer patient's pain is always caused by the cancer. It is important to determine whether the pain arises from the primary tumor and metastases or from secondary complications such as ulceration, infection, obstruction of a hollow viscus, pathologic fracture or compression of nerves by fibrosis or collapse of structural supports. These secondary complications should be treated with local hygienic measures, antibiotics, splints or surgery. Patients with advanced cancer are less able to tolerate pain if they suffer from foul-smelling discharges, dyspnea, dysphagia, nausea and vomiting, intractable cough or hiccups, or profound fear of disfigurement, invalidism, isolation or death. Pain control is easier to achieve when these symptoms are treated and psychological support is given.

It is important to quantitate the pain caused by the tumor and metastases. Get an idea of how frequently pain interferes with daily activities. Ask whether the pain is present throughout the day and whether it keeps the patient from sleeping. How many hours does the patient sleep? What analgesics have been tried? How long does relief last after each dose? It is often helpful to ask patients to rate their pain on a scale from zero to ten, with ten representing the worst pain imaginable. Serial pain ratings can then be used to measure the effect of therapy. Think of pain as a medical problem like any other problem. Quantitate its severity as well as possible and note what treatments have already been

tried; use this information to plan the next phase of treatment. Because pain is so different for each patient, the initial assessment can not provide all the information necessary for formulating a successful pain management plan. It is crucial to reassess pain frequently and modify the pain management strategy as needed.

2. Make a pain management plan.

The goal of therapy is to provide complete pain relief without impairing cognition or other physiologic functions. Sometimes it is not possible to obtain one hundred percent pain relief because as the narcotic brings pain down to a tolerable level, the patient may decide that further analgesia is not worth an increase in narcotic side effects such as constipation or drowsiness. The goal in these patients is to keep pain from interfering with daily activities; this is an achievable goal.

Psychological support is important. Palliative radiotherapy, chemotherapy or surgery should be used if warranted, and secondary complications of the tumor should be treated. Thereafter, narcotics are the mainstay of therapy. Don't waste time on analgesic therapy that has failed in the past. In order to do this, one must be able to compare the potency of different analgesic regimens as described next.

3. Calculate equivalent doses of narcotic analgesics.

When caring for patients with terminal cancer, it is likely that the physician will have to change from one analgesic to another at some point. The most common change is from an analgesic taken by mouth to a parenteral narcotic. Before any narcotic analgesic is marketed, careful potency studies determine how much of the new drug will provide pain relief equivalent to a standard drug such as morphine. Tables showing equivalent narcotic doses are available in the pharmacy literature; unfortunately, they have not yet been included in major medical textbooks. With a narcotic equivalence table, one can calculate the relative potency of different analgesic regimens and derive a drug dose to provide as much or more analgesia as regimens used previously.

As an example, let us compare the Tylox ordered when our patient was admitted, to the Demerol he had been receiving at the referring hospital. We first convert the dose of each drug to Analgesic Units (we define one Analgesic Unit as the amount of analgesia provided by one mg of Demerol administered intramuscularly). Demerol, 100 mg IM every four hours, provides 600 Analgesic Units per day (table 1).[2] Each Tylox capsule contains 4.5 mg of oxycodone hydrochloride, so two capsules by mouth every six hours provide 90 Analgesic Units per day. This Tylox regimen is less than one-sixth as potent as the parenteral Demerol had been and understandably did not relieve our patient's pain.

4. Order analgesics around the clock for constant severe pain.

The pain of advanced cancer is usually constant. When analgesics are administered "p.r.n.," the patient is placed on a roller coaster and forced to reexperience pain before he can receive the next dose of pain medication. The patient anticipates severe pain as analgesia wears off; he or she becomes anxious and pain is more difficult to relieve. It is better to get pain under control and then keep it from recurring by giving analgesics at regular intervals around the clock. Patients often achieve better pain control with a lower narcotic dosage when doses are given around the clock rather than "p.r.n."

Table 1
Narcotic Conversion Table: The relative potency of narcotic analgesics compared to parenteral Demerol

Drug Generic name	Trade name	Analgesic Units* per mg Intramuscular	Oral
Meperidine	Demerol	1.0	0.25
Morphine	—	7.5	1.25
Methadone	Dolophine	7.5	3.75
Codeine	—	0.63	0.38
Oxycodone	Tylox, Percodan	5.0	2.5
Hydromorphone	Dilaudid	50	10

*One Analgesic Unit is the amount of analgesia provided by one mg of Demerol administered intramuscularly. To use this table to calculate doses of equal potency when switching from one narcotic to another, convert each dose (mg) to Analgesic Units. For example, a Tylox capsule contains 4.5 mg oxycodone; two capsules by mouth contain 22.5 Analgesic Units (9 × 2.5) and are equivalent to Demerol, 22.5 mg IM. Morphine, 10 mg IM contains 75 Analgesic Units (10 × 7.5). (Table derived from Lewis BJ, in *Cancer, Principles and Practice of Oncology* (DeVita VT ed), Philadelphia, JB Lippincott Co., 1982, pp. 1658-1665.)

Over seven days the analgesic dose was gradually increased.

Case: *The analgesic dosage was gradually increased (figure 1). Tylox was changed to Demerol 100 mg IM every four hours, then every three hours, and then Methadone, 5 mg by mouth every six hours was added. Pain still recurred before each analgesic dose so on day 4 the physician ordered "Demerol 100 mg IM or by mouth every two hours." Methadone was increased stepwise so that by day 7 the order read "10 mg by mouth every four hours." On day 7 the Demerol could be reduced to 100 mg IM every four hours. Some analgesics were ordered around the clock but others were ordered "p.r.n.," so nurses often withheld analgesics when the patient was vomiting or if he appeared to be asleep. During the hospitalization a total of 15,200 Analgesic Units were ordered, but only 9,307 were actually administered (61 percent).*

An abdominal ultrasound showed that there were no liver metastases but the ascites was found to contain malignant cells. An oncologist felt that the patient did not have long to live and that he would not tolerate palliative chemotherapy. He ws nauseated most of the time.

The doctors recorded the degree of his pain only three times: he was "in pain" on days 2 and 4, and pain was "controlled" at discharge. He was sent home on metoclopramide, 10 mg by mouth every four hours for nausea, Dilaudid, 2 mg by mouth every four to six hours and methadone 10 mg by mouth every four hours.

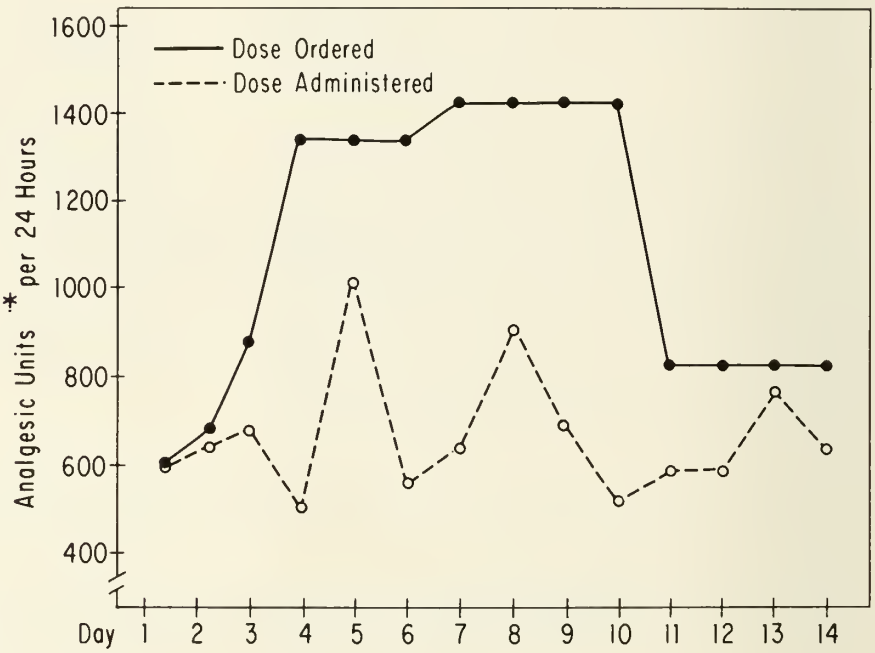


Figure 1. *Pain medication, first admission: Each point represents the sum of Demerol and methadone ordered and administered each day, in Analgesic Units. (*One Analgesic Unit is the amount of analgesia provided by one mg of Demerol administered intramuscularly).*

Comment: Clearly, our physicians, proceeding by trial and error, had a very difficult time controlling the patient's pain. They increased the dosage a little each day and took seven days to reach their maximum (figure 1). They also learned that in order to keep pain from recurring before each dose, the patient needed Demerol every two hours.

Instead of using trial and error, calculate equivalent doses when switching narcotics.

Some of the analgesic orders demonstrate the common difficulty in skillfully exchanging one analgesic regimen for another. For example, Tylox was ordered even though it is much less potent than the parenteral Demerol previously used at the other hospital. Furthermore, the order for Demerol, 100 mg *IM or by mouth,* makes no sense. Demerol by mouth has only one-third the analgesic potency of Demerol administered IM, and is not an equivalent alternative. Worst of all, the Dilaudid prescribed on the day of discharge (120 Analgesic Units per day, figure 2) was not nearly equivalent to the final Demerol dosage in use at the end of his hospitalization (600 Analgesic Units per day). After a long process of trial and error to find a satisfactory analgesic dose, the patient went home on less than half enough analgesic (figures 1 and 2).

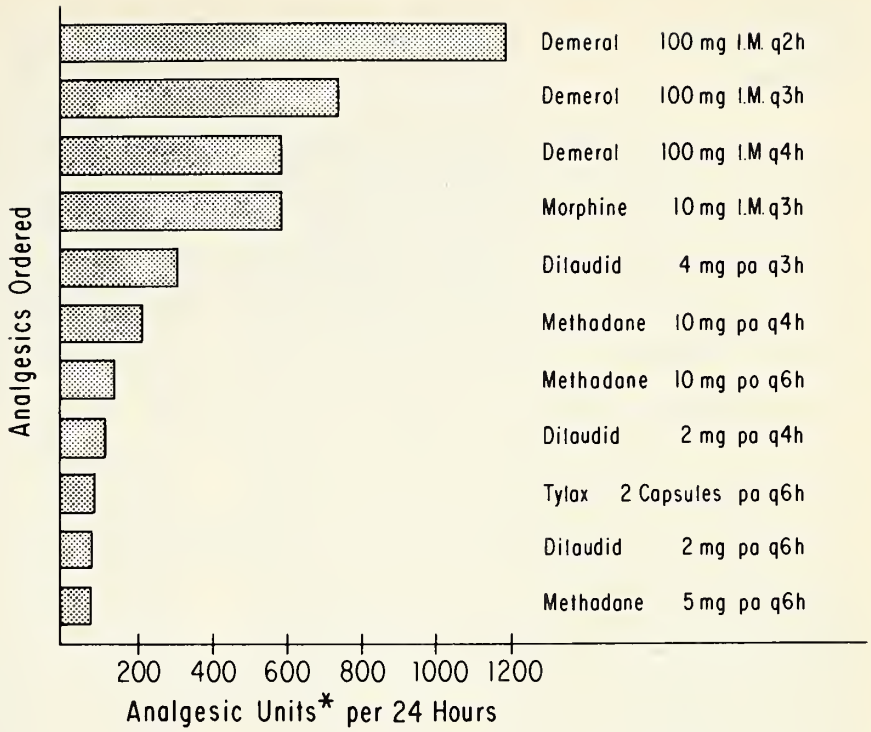


Figure 2. *Relative potency, over twenty-four hours, of analgesics: This figure shows all the narcotic orders that were written for this patient during his two admissions ("po" = by mouth, "q2h" = every two hours.) (*One Analgesic Unit is the amount of analgesia provided by 1 mg of Demerol administered intramuscularly.)*

More Pain Management Strategies

5. Young patients require analgesics at short intervals.

Narcotics have a shorter duration of action in young patients. The duration of action of morphine in patients under age twenty-nine is about 2.5 hours, whereas it is nearly four hours in patients over age seventy.[3] Demerol has an even shorter duration of action than morphine, so it should be prescribed at intervals of less than three hours and the patient should be checked frequently to see if pain recurs before the next dose.

Demerol relieved our patient's pain for only two hours. Although this may indicate that his hepatic function was good (he had no liver metastases), the patient also became more and more anxious because pain returned before each scheduled dose making his pain more difficult to relieve. To avoid analgesic peaks and valleys, it is better to give analgesics at frequent intervals or to use longer-acting narcotics whenever possible.

6. Use long-acting analgesics.

Several long-acting analgesics are available and have been used successfully to manage severe pain in terminal cancer; most of these can be given by mouth. The Brompton Cocktail (originally a solution of heroin, cocaine, chloroform water, alcohol and a flavoring agent) has become well known because British hospices have used it with great success. In this country, oral morphine solution is generally used and seems just as effective. It is long-acting when compared to parenteral Demerol, with a duration of action of four to five hours. It is consistently absorbed from the gastrointestinal tract, although larger doses are required by mouth than parenterally. When used in doses of 20 to 120 mg five to six times a day, patients achieve good pain relief but experience transient drowsiness for the first 24 hours. Nausea and vomiting may also occur but can be treated by adding an antiemetic to the mixture. Since the solution is taken by mouth, patients can be treated at home.[4] As an alternative, Methadone provides even longer analgesia (four to eight hours), is very cheap and can be administered by mouth or parenterally. Wide fluctuations of blood analgesic levels are avoided, preventing the potential complication of physiologic withdrawal in patients who require narcotics for weeks or months.

A distinct disadvantage of short-acting analgesics such as parenteral Demerol is that nurses can not always administer them on time. This may partially explain why our patient received only sixty-one percent of the narcotic Analgesic Units that were ordered. Unless there is an excellent nurse-patient ratio or the patient is attended by a family member at home, it is wise to prescribe a narcotic with a longer duration of action than Demerol.

7. Wake the patient if necessary.

Most nurses will not wake patients to give analgesics, although they will wake them to give antibiotics or other drugs. Severe pain is more difficult to alleviate after an analgesic dose has been withheld. On several occasions when our patient's analgesics were withheld because he was sleeping, he woke to ask for them only thirty minutes to an hour later. It is better to give analgesics at fixed intervals around the clock to keep severe pain from recurring a short time later.

The patient was readmitted with severe pain.

Case: *Three weeks later the patient was readmitted with ascites, edema and severe pain. His physicians made explicit plans to evaluate and treat the ascites and edema, but ordered Dilaudid, 2 mg, one to two tablets by mouth every three to six hours as needed for pain, and methadone, 10 mg by mouth every four hours around the clock. Dilaudid was never given. Although metaclopramide, 10 mg by mouth four times per day, was ordered for vomiting, nausea and vomiting continued and the patient could not retain the methadone. When pain control proved unsatisfactory, parenteral Demerol was started and the dose was rapidly increased to 100 mg IM every two hours (figure 3).*

The patient continued to complain of severe pain so on day 4 Demerol was stopped and morphine, 10 mg IM every three hours, was begun. Parenteral vistaril was given with each dose; afterwards the patient was more comfortable. He died three days later.

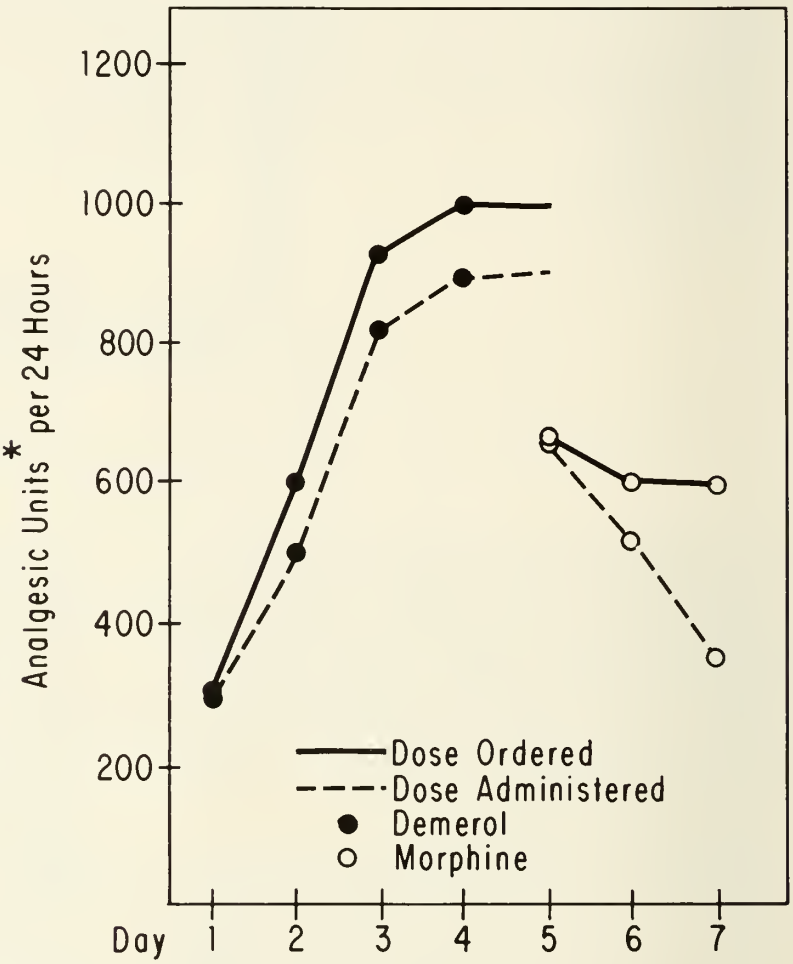


Figure 3. *Pain medication, second admission: Each point represents the amount of Demerol or morphine ordered and administered each day, in Analgesic Units(*) (*One Analgesic Unit is the amount of analgesia provided by 1 mg of Demerol administered intramuscularly.).*

Analgesic orders were vague.

Comment: Again, the patient's primary physician failed to make a pain assessment or plan. The orders reflect this: the Dilaudid order was so broad that the analgesic decision was essentially delegated to the nurses. They could give him as much as two tablets every three hours (320 Analgesic Units daily, figure 2) or as little as one tablet every six hours (80 Analgesic Units daily). Even worse, because the order was "p.r.n.," the nurses also could have chosen to give no Dilaudid at all. That is what happened.

Nausea and vomiting interfered with pain management.

The Dilaudid order was worthless because Dilaudid was never given. Moreover, the methadone order was unsatisfactory because the patient was vomiting and could not take the drug by mouth. Vomiting was not controlled until a parenteral antiemetic was given round the clock.

The physicians went narcotic-shopping.

When the patient was still in pain on Day 4, the physicians decided Demerol had "failed" and abandoned it. But since they did not calculate equivalent narcotic dosages they ordered a dose of morphine that was even less potent than the Demerol that had "failed." Fortunately, the patient became more comfortable during the last three days of his life, possibly because his nausea was controlled or because parenteral morphine has a slightly longer duration of action than Demerol.

8. Take charge of pain management: Write clear analgesic orders.

A physician who writes narcotic orders that allow a wide discretionary range in dose and dosing interval essentially abdicates his or her responsibility to manage pain. The responsibility is left with the nurses, who rotate every eight hours, and who receive little training in pain management. There may be no primary nurse. Sometimes there are too few nurses on each shift to make good pain assessments and to administer analgesics frequently and promptly.

Pain is managed most successfully by someone who takes a firm leadership role, decides on a definite pain control plan, assesses the patient frequently and adjusts the regimen as needed. When there is a primary nurse skilled in pain management and there is a favorable nurse-patient ratio, the nurse can certainly assume a large part of this responsibility. But in many hospitals such ideal conditions do not exist. It is then better for the physician to take charge of pain management by writing clear analgesic orders that do not allow a discretionary range in dosage. Based on how much pain is relieved by each dose, and how long relief lasts, the physician should frequently adjust the amount of narcotic per dose and the interval between doses.

9. Control nausea and vomiting.

Many cancer patients are plagued by nausea and vomiting. Some patients have anticipatory vomiting on the day they are scheduled for chemotherapy. Nausea and vomiting can be caused by chemotherapeutic agents or by the tumor, especially if the tumor involves the stomach. Severe pain can cause nausea and vomiting. It is difficult for the nauseated patient to tolerate oral analgesics; therefore prescribe parenteral narcotics until these symptoms are under control. The patient may require parenteral antiemetics around the clock. Narcotics themselves stimulate the brainstem's chemoreceptor trigger zone and cause nausea and vomiting in some people. Although it can be difficult to sort out just what is causing a cancer patient's nausea, narcotic-induced nausea may resolve after several doses and it can generally be improved or prevented by lying in bed.

Standard antiemetics such as Compazine, Phenergan or Tigan may adequately control nausea and vomiting. These drugs are available in suppository and injectable preparations as well as in oral form. Antiemetic suppositories can be given around the clock to control persistent nausea and vomiting and are especially useful for outpatients or for patients who do not tolerate injections because of diminished muscle mass. The vomiting induced by chemotherapeutic agents, especially Cisplatin, Adriamycin and nitrogen mustard may be refractory to standard antiemetics; clinical trials using haloperidol, droperidol, cannabinoids and metoclopramide have shown that these may be somewhat more effective.[5]

10. Use oral analgesics.

Once nausea and vomiting have been controlled, the patient should be started on oral analgesics. For over ten years, British hospices have reported that severe cancer pain can be controlled to the end or near the end of life with oral analgesics. Oral analgesic strategies fail most commonly because the oral regimen chosen provides many fewer Analgesic Units than the parenteral regimen had provided (figure 2). This problem can be avoided by calculating equivalent doses. When the patient has required large doses of parenteral narcotics, choose an oral analgesic such as morphine elixir or methadone; the dosage of Tylenol #3, Tylox or Percodan is limited because of the Tylenol or aspirin they contain. If dysphagia is present, morphine elixir may be easier to swallow than methadone tablets. After pain has been controlled with oral analgesics around the clock, the dose or dosing interval often can be decreased because anxiety and pain have decreased. After several days, methadone dosage may need to be reduced because tissue storage sites become saturated and half-life increases. This is especially true for patients with metastases to the liver or brain or with renal insufficiency. The patient will become sleepy or confused as methadone accumulates; this is best treated by withholding methadone for twelve hours then restarting it at a lower dose or longer dosing interval.[6]

Oral analgesics should be used for several reasons: They have a somewhat longer duration of action than parenteral narcotics and provide smoother analgesia because rapid swings in blood analgesic levels are avoided. Parenteral Demerol has such a short duration of action that swings in blood levels are especially pronounced. Oral analgesics spare patients from repeated painful injections, especially emaciated patients who have diminished muscle mass. Importantly, oral analgesics allow patients to go home and spend time with loved ones in a familiar environment. At home patients no longer have to compete for the attention of busy nurses and they or their family members can promptly administer pain medication as directed.

If the patient is unable to take medication by mouth, sometimes pain can still be managed at home by using analgesic suppositories. Dilaudid is available in 3 mg suppositories and pharmacists can prepare other narcotics in suppository form. Dilaudid by suppository provides 25 Analgesic Units per mg.

11. Don't go narcotic-shopping.

We often get angry at patients who shop from doctor to doctor and never stay with any treatment long enough to benefit from it. Doctors do the same thing when they switch analgesics, hoping that the new one will somehow be "stronger," "faster" or "better." Many people think morphine is "stronger" than Demerol, and that is apparently why our physicians switched to morphine when Demerol had not "worked" after four days. But morphine is not intrinsically "stronger" than Demerol; equivalent doses can be determined by calculating Analgesic Units (table 1). Any experienced physician knows that pain man-

agement is complex and that no single drug will make it simple. Doctors should never need to change narcotics out of blind desperation or a false hope that a "new" drug will be "better" when the real problem is incomplete assessment of patients, broad discretionary analgesic orders or drug administration schedules that allow too small a dose at too long an interval.

Summary

The American College of Physicians recognizes that internists need to learn more about narcotics and how to use them to treat severe, chronic pain in terminal cancer.[1] Pain control for these patients is a difficult but achievable goal. It is difficult because each patient is different; pain is not like pneumococcal pneumonia where a fixed dose of antibiotic will make most patients better. It is a time-consuming process because frequent patient assessment and regimen adjustments are required, but it is worthwhile because much suffering can be relieved. Physicians can learn to control pain by using several strategies to avoid common pitfalls (table 2).

The analgesic prescription for an individual patient must take into account the severity of pain, the patient's age, and whether the patient has nausea or vomiting. Determine the severity of pain through an accurate pain assessment: learn which analgesics have already been tried; use the information to make a pain control plan. Use palliative radiotherapy, chemotherapy or surgery when indicated and look for secondary complications such as pathologic fractures.

The primary physician should take charge of pain management and write precise analgesic orders. Most cancer patients will have better pain control if narcotics are given around the clock instead of "p.r.n.," because this prevents pain and anxiety from recurring before each analgesic dose. If necessary, wake the patient to give analgesics on schedule. Choose long-acting analgesics, especially when liver and kidney function is good and when the patient is young. Control nausea and vomiting.

Become skilled in switching narcotics or routes of administration by learning to calculate Analgesic Units using table 1. This is the key to using narcotic analgesics proficiently. One doesn't need to hop arbitrarily from narcotic to narcotic. One analgesic is not "stronger" than another, but some narcotics are traditionally prescribed at doses that deliver more Analgesic Units than others. Even morphine, which many physicians believe is not effective when given by mouth, can provide good analgesia if enough is given to make up for decreased gastrointestinal absorption. High narcotic doses may be required to achieve pain relief; the doctor will need to monitor these patients closely for side effects such as constipation and confusion. By calculating Analgesic Units, it is possible to avoid lowering your patient's analgesic dosage inadvertently when you must change from one narcotic to another.

Table 2
Strategies for Using Narcotics to Control Severe, Chronic Pain in Terminal Cancer

Make a pain assessment
Make a pain control plan
Take charge of pain management
Write precise analgesic orders
Calculate Analgesic Units
Switch drugs using equivalent doses
Avoid "p.r.n." dosing
Wake the patient if necessary
Use long-acting analgesics
Use short intervals for young patients
Control nausea and vomiting
Use oral analgesics
Don't go narcotic shopping

Above all, it is never appropriate to withhold adequate doses of analgesics out of a misplaced fear of narcotic addiction. When curative therapy has failed, pain management is the most important thing the physician can offer a cancer patient, remembering his or her duty to cure only sometimes, but to comfort always.

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SCIENTIFIC ARTICLE

The Clinical Management of Sore Throat: A Comparison of Three Ambulatory Settings

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SORE THROAT is a common patient complaint, but its proper management is still a matter of debate. Respiratory infections, many of which present with a sore throat, are the number one cause of acute illness in the U.S. and sore throat is the fourth most common symptom presenting to medicine practices in the U.S.[1-2] Few acute respiratory diseases can be treated and fewer still have important long term morbidity. Streptococcal pharyngitis, however, is both treatable and a precursor to acute rheumatic fever. The diagnosis and treatment of streptococcal pharyngitis is an occasion for the continuing debate over the clinical management of sore throat.

In the past, medical opinion has urged the culturing of all patients presenting with a sore throat and the treatment of all positive cultures with antibiotics as the best means for minimizing the risk of rheumatic fever.[3] Recent studies have recommended different culture and treatment strategies. In a study of the families of children with rheumatic fever, Peter and Smith proposed throat cultures for children with predominant sore throat symptoms and a temperature of 37.3°C or greater.[4] Forsyth suggested a cluster of symptoms (fever, exudative pharyngitis, cervical adenitis) as a clinical guide, reserving throat culture only in patients at high risk for acute rheumatic fever. This approach provided a combination of accurate case finding and rational use of laboratory services.[5] Tompkins, Burnes and Cable have outlined three culture-treatment strategies for endemic pharyngitis based upon the percentage recovery of bacillus from the cultures.[6] These conflicting opinions have prompted one author to conclude that "there are no firm guidelines for culturing."[7]

Given that the normative models (what physicians *should* be doing) lack consensus, what *are* physicians doing when patients present with a sore throat? To answer that question, we observed the clinical management of sore throat at three different ambulatory care sites — a Family Practice Center, a Pediatric Screening clinic, and a general medicine Walk-In clinic — in a university teaching hospital.

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Methods

The setting for this study was the North Carolina Memorial Hospital, a public teaching and referral hospital in Chapel Hill, North Carolina. At NC Memorial, the Family Practice Center sees patients of all ages for both acute and chronic problems. Faculty and residents from the Department of Family Medicine comprise the Center's physician staff. In 1981-82, 16,041 patients were seen in the Center.

The Pediatric Screening clinic provides round-the-clock consultations for unscheduled patients aged one month to 16 years. In 1981-82, the faculty attendings and the resident staff from the Department of Pediatrics saw 8,349 patients. The Walk-In clinic sees unscheduled adult patients on weekdays for non-emergent medical complaints. The staff consists of second year residents from the Department of Medicine under the supervision of a faculty attending physician. Patient visits during 1981-82 numbered 6,138.

The data for this study were drawn from patients visiting the Family Practice Center in March 1982 and from patients attending the Pediatric Screening and Walk-In clinics in December 1981 and January 1982. To be eligible for the study, patients either had to be making a first visit for a problem that included a complaint of a sore throat or had to be making an initial visit for a problem that led to the ordering of a throat culture. A "sore throat" included complaints of "scratchy," "dry," "irritated" and other common manifestations of an infected or swollen throat.

Origins of the study sample are summarized in figure 1. During the month of data collection, the Family Practice Center had 1,629 patient visits. A presenting complaint log and a record of all cultures identified 88 eligible patient visits (5%). Four patients' records were unobtainable, reducing the final Family Practice Center sample to 84 encounters (95% of eligible).

In Pediatric Screening, log books of patients' presenting complaints and lab cultures identified as eligible 142 (11%) of the total 1,254 patient visits during the two month study period. To equalize sample sizes by clinic location, a random 50% sample of all eligible patient visits (n = 69) was selected for inclusion in the study.

During the two month study period, 1,035 visits took place in the Walk-In clinic, but records for review were available for only 879 (84%) of the encounters. Of this number, 70 (8%) met the study criteria.

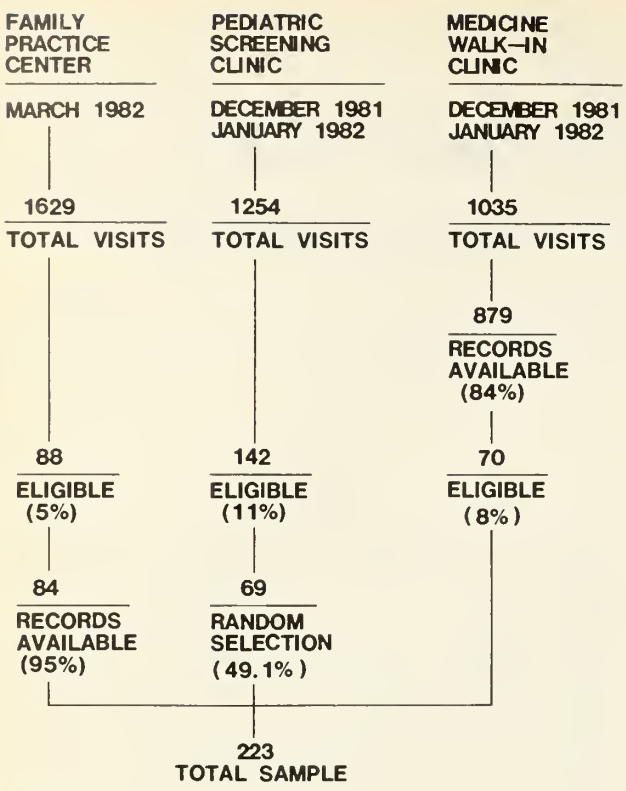


Figure 1

Total sample size for the study, then, was 223 patient visits representing 74% of all patient visits eligible for the study.

The medical records of all 223 study patients were reviewed for demographic and clinical information for the encounter of interest. Patients who were between four and 30 years of age (inclusive) were classified as "at risk" for rheumatic fever due to age. Clinical variables fell into three categories. (1) Presentation data included symptoms, exposure to strep throat and physical findings (erythema, exudate, tonsilar enlargement and cervical adenopathy). (2) Management data included information about throat cultures (obtained/results), treatment (if/when/with what), and follow-up. (3) Physician data indicated the physician's diagnosis.

Results

Patients presenting with sore throat to the three different settings were somewhat dissimilar (table 1). Pediatric patients more often presented with a sore throat. Family Practice patients lived closer to the hospital and were more often white than were the patients of the other two settings.

Family physicians cultured virtually every patient (81/83, 98%) who presented with a sore throat. Eight of the cultures proved to be positive (figure 2). Pediatricians also ordered cultures on a high percentage of patient encounters (61 of 69, 88%), but nearly half (29/61, 48%) were positive for streptococcus A. Internists in the Walk-In clinic cultured only about half (36/70) of the patients with sore throat presentation. Only three of these cultures were positive.

Differences in cultures obtained appeared to be related to the patient's symptoms (table 2). Among patients whose major symptom was only a sore throat, physicians from all settings ordered throat cultures in a high percentage of patients. However, when the sore throat was accompanied by other symptoms, especially those suggesting upper respiratory problems, internists ordered throat cultures about half as often as pediatricians and family physicians, even among patients considered to be at risk by age for rheumatic fever.

Treatment of patients with a presentation of sore throat also differed across the three settings (table 3). In the Walk-In clinic, where cultures were done least often, internists treated nine of 33 (27%) patients without cultures and seven of 33 (21%) patients with negative cultures. In Pediatric Screening, where almost all patients were cultured, three of eight patients (38%) without culture and four

Table 1
Characteristics of Patients Presenting with Sore Throat at Three Different Ambulatory Settings

Percent of Visits With Sore Throat Presentation	Family Practice Center (n = 84) 5%		Pediatric Screening (n = 69) 11%		Medicine Walk-In (n = 70) 8%	
	n	%	n	%	n	%
Race:						
Non-white	12	14	35	51	42	60
White	72	86	34	49	28	40
Gender:						
Male	35	41	34	49	22	31
Female	49	59	35	51	48	69
Age:						
Median		21		8		27
Range		3-77		2-38		16-77
At Risk (4-30)	58	69	58	84	43	61
Distance from Setting*						
≤30 minutes	79	94	48	71	43	62
>30 minutes	5	6	20	29	26	38

* One case missing for Medicine Walk-In and Pediatric Screening.

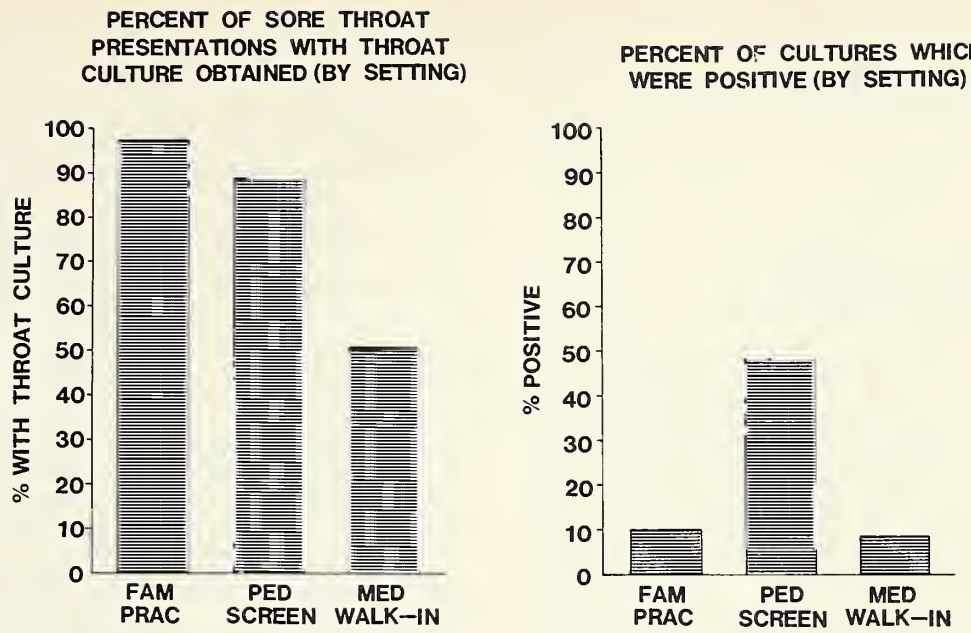


Figure 2

Table 2
Throat Cultures Obtained by Presenting Symptoms and Age Risk At Three Different Ambulatory Settings*

Symptoms:	Family Practice Center pts	n	%	Pediatric Screening pts	n	%	Medicine Walk-In pts	n	%
Sore Throat Only									
At Risk Patients	13	13	100	13	10	77	9	8	89
All Patients	19	19	100	13	10	77	10	8	80
Sore Throat and URI									
At Risk Patients	27	25	93	17	14	82	24	11	46
Not At Risk Patients	38	36	95	21	17	81	39	15	38
Sore Throat and Other Symptoms									
At Risk Patients	6	6	100	13	13	100	8	5	63
Not at Risk Patients	9	9	100	14	14	100	18	10	56

* Missing from this table are those cases where there was evidence of a lab test but where no record of the clinic note (for symptom description) was available.

Table 3
Antibiotic Treatment of Patients By Throat Culture In Three Different Ambulatory Settings

Throat Culture:	Family Practice Center n	%	Pediatric Screening n	%	Medicine Walk-In n	%
No Culture Obtained						
Total Patients	2	100	8	100	33	100
Treated	0	0	3	38	9	27
Not Treated	2	100	5	62	24	73
Positive Throat Culture						
Total Patients	7	100	29	100	3	100
Treated	5	71	22	76	2	67
Not Treated	2	29	7	24	1	33
Negative Throat Culture						
Total Patients	69	100	28	100	33	100
Treated	24	35	4	14	7	21
Not Treated	45	65	24	56	26	79

Table 4

Point of Treatment for Patients Suspected of Strep Throat Across Three Different Ambulatory Settings

	Family Practice Center		Pediatric Screening		Medicine Walk-In	
	n	%	n	%	n	%
Patients with Throat Cultures Obtained	36	100	57	100	76	100
Total Patients Treated with Antibiotics	9	25	26	46	29	38
Treated with Antibiotics on First Visit	9	100	8	31	24	83
Treated with Antibiotics on Follow-up Visit (2-3 days)	0	0	18	69	5	7

of 28 patients (14%) with negative cultures were treated with antibiotics. Family physicians did not treat either of the two patients without a throat culture, but they did treat 24 of the 69 patients who had a negative culture. In a few cases, treatment included antibiotics prescribed for other concurrent infections (e.g., otitis media or sinusitis).

According to the medical records a number of patients with positive cultures from all settings did not receive antibiotic treatment (table 3). Pediatric Screening had the highest rate of untreated positives, 24% (7/29). Given the overall occurrence of sore throat presentation in the Pediatric Screening Clinic and the occurrence of untreated positives, it would follow that 12 out of every 1,000 patient visits would result in an untreated streptococcal infection.

For patients with throat cultures, pediatricians more often opted for a delayed treatment strategy than did the physicians in the other two settings (table 4). Of the 36 Walk-In patients with throat cultures, nine (25%) were treated, all on the initial visit. Family physicians more often treated patients with cultures (29/76, 38%), but again the vast majority were treated on the initial visit (24/29, 83%). In Pediatric Screening, on the other hand, 26 of 57 (46%) patients with cultures were treated, but only 8 of the 26 (31%) received treatment on the first visit.

Discussion

Observed management of sore throat in a university teaching hospital very much reflected the current debate over the normative management of sore throat. Physicians in three ambulatory care settings had different approaches to the problems of culture and treatment.

This study has several limitations. First, the small sample size did not permit comparisons of treatment strategies across all three settings while controlling for risk factors, cultures (degree of positivity), presenting symptoms and physical findings. Second, because physicians do not always record all of their activities, written medical records (charts, logbooks) conservatively measure physician activity and generally overestimate omissions in care, such as failure to treat patients with positive throat cultures. Finally, sore throat symptoms, throat culturing, and streptococcal pharyngitis are subject to seasonal fluctuations with peaks in the winter months. The data for this study were taken from cases appearing in peak months: December, January and March. Clinical management of sore throat may differ in other months of the year. Nonetheless, these data do suggest that in actual practice, physicians disagree on the proper management of sore throat.

In this study family physicians and pediatricians cultured almost every patient presenting with a sore throat while internists cultured more selectively. This strategy may be fairly common. In a 1978 survey, Gillette found that 66% of family practice residency programs used throat cultures in managing adult patient sore throats, while only 36% of practicing physicians did so.[8] A recent statewide study in Rhode Island estimated that approximately 50% of all physicians cultured every sore throat presentation, and that about 70% of all patients with a sore throat were cultured.[9] In the same study, pediatricians cultured more often than did non-pediatricians, but there was no reported difference between internists and family physicians.

Once a culture was obtained, family physicians and internists were equally likely to treat the patient without a culture result. Pediatricians were more likely to postpone treatment until the results were known. By contrast, in the Rhode Island study, pediatricians were more likely to treat on the initial visit, although the vast majority (87%) of all physicians reported likely initial visit treatments.[9]

None of the physician groups in this study closely followed the normative management model suggested by Tompkins et al.[6] Family physicians adopted a strategy of culture and treat on the first visit, a practice that may have generated additional costs. A similar pattern has been found among Emergency Room physicians.[10] Internists, who more selectively cultured and treated, tended toward Tompkin's strategy C (neither culture nor treat), perhaps following guidelines for management based upon physical findings.[12-15] Pediatricians, however, appeared to have adopted a strategy completely opposite to that proposed by Tompkins. Whereas the 48% positive throat culture rate in the Pediatric Screening clinic would have suggested to Tompkins that patients should be treated without culture, pediatricians cultured almost all patients and then treated all positive cultures.

The cost implications for the patient (time and travel) likely vary from setting to setting and should have some influence upon the physician's selection of a management strategy. For example, in the Family Practice Center where the vast majority (94%) of the patients live within 30 minutes of the clinic and where the positive culture rate is relatively low (10%), a strategy of a return visit treatment based upon a culture result would seem appropriate. On the other hand, in Pediatric Screening, where a larger percentage of the patients come from further away (29% more than 30 minutes), where the positivity rate is much higher (48%), and where compliance with oral antibiotics is likely

low, a more appropriate strategy would seem to be treatment on the initial visit, especially in those cases falling into high risk categories defined by age, exposure, symptoms and physical findings. Pantell's multi-factorial analysis of seven different strategies for managing sore throat supports this selective, population-specific approach on a cost effective basis.[11]

Debate over the proper management of sore throat is not just a tempest in academic medicine's teapot. Traditionally, the principal aim of sore throat management has been to identify and treat streptococcal pharyngitis so that it will not later develop into a more serious disease, such as acute rheumatic fever. However, acute rheumatic fever is no longer the scourge it once was. Twenty years ago, Gorlis et al estimated the incidence of new acute rheumatic fever to be 24 cases per 100,000. More recent studies in metropolitan Memphis, Tennessee and in Rhode Island have reported much lower incidence rates: .64 per 100,000 and .2 per 100,000 respectively.[9, 16] This decline in acute rheumatic fever actually became apparent prior to the widespread introduction of antibiotics. Thus, while the treatment of streptococcal pharyngitis has surely contributed to the continuing decline in acute rheumatic fever, the extent of that contribution is unknown. Further, although the direct costs of culture and treatment are relatively small for any one patient, the accumulated nationwide costs are quite substantial. Serious questions exist about the cost-effectiveness of culturing and treating sore throats.

This study took place in a university teaching hospital among physicians with a variety of clinical experiences. Life-long practice habits are likely formed in these training settings, most often with residents adopting the normative behaviors demonstrated by the senior faculty. Although management of sore throat within each of the three settings observed showed internal consistency, none of these reflected either medically optimal or cost-effective patterns of management. Particularly in an era of increasing cost consciousness, teaching centers must focus on both these factors if future primary physicians are to be trained to function effectively. Given that physicians currently do not agree, in either a de facto or a de jure sense, on the proper management of sore throat, a comprehensive reappraisal of this aspect of clinical medicine is in order.

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Thrombolytic Therapy

Julie Jacobs

Dear Readers:

The Duke Medical Center Pharmacy will publish reviews of therapeutic agents commonly prescribed within the hospital setting in the form of a special column for the North Carolina Medical Journal. *These reviews, written by pharmacy residents and clinical pharmacists, are regularly published in the Duke Hospital Drug Information Bulletin. Each is reviewed by staff physicians with expertise in the area each article addresses. The editors welcome reader comments and suggestions.*

Christine C. Rudd, Pharm. D.
Richard Drew

THROMBOLYTIC therapy represents a new medical approach to the treatment of patients with thromboembolic diseases. Conventional anticoagulant therapy with heparin or coumarin derivatives does not bring about the dissolution of thrombi and emboli. A lysis of clots would permit a return of blood flow through the affected vessels and reduce the pain and swelling associated with the destruction of venous valves in patients with deep venous thrombosis. Thrombolytic therapy may be of benefit in decreasing the long-lasting ill effects associated with thrombosis and embolism. It in no way replaces or minimizes the use of anticoagulants for the continued care of such patients, but offers an alternative approach with considerable advantages in terms of long-range prognosis for such diseases.

Two thrombolytic agents are available in the United States for clinical use. Streptokinase is marketed as Streptase (Hoeschst-Roussell Pharmaceuticals, Inc.) and Kabikanase (Kabi Group). Urokinase is marketed as Abbokinase (Abbott Laboratory) and Breokinase (Breon Labs).

Streptokinase was discovered in 1933 by Tillett and Garner when they observed that a filtrate of Group C beta-hemolytic streptocci lysed a human plasma clot.[1] Subsequent studies helped to characterize the interaction of the extract with the fibrinolytic system and showed that the activator substance acted on plasminogen to produce plasmin, an active enzyme.[2] This activator was named "streoptokinase." In 1959, Johnson and McCarty successfully lysed thrombi that had been experimentally induced in forearm veins of volunteers.[3]

MacFarlane and Pilling isolated a similar substance from human urine in 1946.[4] This substance was given the name "urokinase" by Sobel and his colleagues.[5] Further investigations demonstrated that urokinase was also a plasminogen activator. Sherry et al. subsequently provided important pharmacologic and clinical information that led to the experimental use of urokinase for therapeutic thrombolysis.[6] By 1960, Ploug and Kjeldgaard had developed purification methods for isolation of urokinase from urine in a form suitable for clinical investigations.[7] This urokinase possessed high specific activity; it was free of contamination and was also virus-inactivated, nontoxic, and nonpyrogenic.

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Mechanism of Action

While heparin has no direct effect on formed thrombi, streptokinase and urokinase actually promote dissolution of a thrombus by stimulating the conversion of fibrin-bound inactive proenzyme plasminogen to active enzyme plasmin, where it is protected from circulating inhibitors (see figure 1). Streptokinase does this indirectly by forming an activator complex with plasminogen, while urokinase acts directly.[8-10] Plasmin is a proteolytic enzyme that acts in two areas. Locally, it promotes fibrin digestion, resulting in dissolution of the thrombus.[8-10] Systematically, biochemical changes in the blood result in a "lytic state" which can be defined as a decrease in plasma plasminogen and fibrinogen, and a prolonged prothrombin or thrombin time, thus increasing the potential for hemorrhage.[8-10] Natural protein inhibitors (solid cross bars, figure 1) of activation are overcome during the induction of the lytic state of infused activators because the amount of drug used in standard treatment regimens far exceeds the inhibiting potential of these proteins.[11]

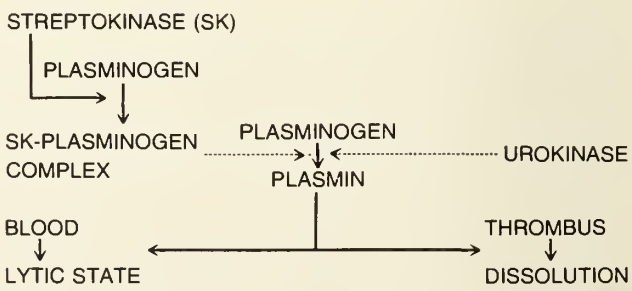


Figure 1.[11] *Action of Streptokinase and Urokinase in achieving thrombolysis.*

Pharmacokinetics

The plasma clearance rates of streptokinase have been studied in both normal and immune man.[12] Intravenously injected streptokinase is cleared from the circulation at two distinct rates. The "fast" rate (18 minutes) appears to be a consequence of the combination of streptococcal antigen with its antibody and the subsequent clearance of this complex.[12] The "slow" rate (83 minutes) occurs in the absence of plasma antibody and may be due to activity of the reticuloendothelial system.[12] The fibrinolytic effect disappears within a few hours after discontinuation of the infusion, but prolonged thrombin time may persist for 12-29 hours because of a decrease in plasma levels of fibrinogen and an increase in the amount of circulating fibrinogen degradation products.[13]

Following intravenous administration, urokinase has a circulating half-life of 20 minutes or less.[14] As with streptokinase, fibrinolytic activity may persist for 12-24 hours after discontinuation of the infusion.[14]

Kinetic data concerning the use of these agents in patients with renal or hepatic disease are unavailable because of the relative contraindications to their use in this population.

Therapeutic Uses

The clinical indications of thrombolytic therapy have been defined by the Food and Drug Administration. On the basis of results from clinical investigations, streptokinase has been approved for treatment of the following conditions: acute pulmonary embolism and deep-vein thrombosis (within seven days of onset of symptoms), arterial thrombosis, acute myocardial infarction, and occlusion of access shunts and intravascular or cavity catheters.[15] Urokinase may be used in cases of acute pulmonary embolism (within seven days of onset of symptoms) and occlusion of access shunts and intravascular or cavity catheters.[14]

Most clinical studies have employed similar methodologies; thrombolytic agents have been administered into a peripheral vein or directly into the pulmonary artery and continued for 12 to 72 hours. Heparin has also been given for five to seven days followed by oral warfarin therapy. Many of the studies also included a control group treated with heparin only in conventional doses. Diagnosis of pulmonary embolism was most often confirmed by pulmonary angiography and lung scans. In most trials, improvement was measured by the mean reduction in clot size in the post-infusion angiogram compared with the preinfusion angiogram.

Pulmonary Embolism

Both streptokinase and urokinase have undergone extensive clinical evaluation in the treatment of pulmonary embolism in Europe and the USA in the past decade. Most of the early studies were uncontrolled and/or nonrandomized; therefore an accurate comparison between heparin and thrombolytic agents was not available. The most significant data comparing these two agents with heparin in the treatment of pulmonary embolism were produced by two large multicenters' randomized studies sponsored by the National Heart and Lung Institute (NHLI), the Urokinase Pulmonary Embolism Trial (UPET) and the Phase II Urokinase-Streptokinase Pulmonary Embolism Trial.[16, 17]

Phase I of this trial compared heparin with urokinase therapy in 160 patients with angiographically demonstrated pulmonary embolism.[16] A well-documented clinical episode suggesting that pulmonary embolism had occurred within five days of the institution of therapy was necessary for patient eligibility. Patients receiving urokinase were given a loading dose of 2,000 CTA (Committee on Thrombolytic Agents) units/lb of body weight followed by 2,000 CTA units/lb/hr, while the patients given heparin received a loading dose of 75 units of heparin/lb of body weight followed by 10 units/lb/hr for a total of 12 hours. After termination of the 12-hour infusion, all patients received heparin intravenously for a minimum of five days followed by orally administered warfarin therapy. Urokinase was found to be significantly superior to heparin in accelerating the resolution of pulmonary embolism. Especially important was the fact that patients with massive pulmonary embolism accompanied by shock had the greatest degree of resolution ranging from 33.4 to 68.6 percent. However, the two-week mortality rate for both regimens was approximately equal.

Phase II of this trial sought to determine whether 24 hours of urokinase increased the amount of clot resolution beyond that found after 12 hours and how 24 hours of streptokinase compared with 24 hours of urokinase.[17] The eligibility criteria for admission of patients into this trial were very similar to those established in the Phase I trial. Patients receiving streptokinase were administered a loading dose of 250,000 units of streptokinase intravenously over 20-30 minutes, followed by 100,000 units/hr by a constant infusion pump for 24 hours. Patients given urokinase received a loading dose of 2,000 CTA units/lb/hr for either 12 or 24 hours. After termination of each infusion, all patients received heparin intravenously for a minimum of five days, followed by oral doses of anticoagulants. The mean improvement in pulmonary arteriogram and hemodynamic variables, as well as the incidence of hemorrhagic complications and recurrence of pulmonary embolism, was not significantly different among treatment groups. The two-week and six-week mortality rates also were not significantly different. Thus the data from this trial indicate no further benefit from 24 hours of urokinase than with 12 hours and suggest that the efficacy of urokinase and streptokinase is similar.

In a recently published report, Sharma et al. selected 40 patients from the NHLI studies and observed the effects of thrombolytic agents on small peripheral pulmonary clots that were beyond the resolving capabilities of angiography or scanning.[18] Pulmonary capillary blood volume and total diffusing capacity of the lung remained unchanged in the heparin group, but improved significantly in the thrombolytic group at two weeks and one year.

A study by Tibbutt et al. compared streptokinase with heparin therapy in 30 patients with life-threatening pulmonary embolism.[19] Two patients in the streptokinase group and five in the heparin group were excluded because they failed to complete 72 hours of therapy. In mean angiographic scores, response to treatment was clearly better with streptokinase. The heparin group, however, consisted of a greater number of severely ill patients. A six-month

Table 1[13]
Summary of Clinical Trials Utilizing Urokinase, Streptokinase, and Heparin in Pulmonary Embolism

Reference/Study Design	Number of Patients	Drug	Mean Lung Scan Resolution (%)	Angiography (mean decrease in size of clots-%)	Mortality (%)
Co-op study[16]	160	Urokinase	22.1		7.4
ramdomized, controlled		Heparin	8.1		8.9
Co-op study[17]	167	Urokinase ×24h	29.2		9.0
randomized, controlled		Urokinase ×12h	20.0		9.0
		Streptokinase ×24h	18.5		9.0
Tibbutt et al[19]	23	Streptokinase		61.0	0
randomized, controlled		Heparin		15.0	8.0
Ly et al[22]	20	Streptokinase		52.3	0
randomized, controlled		Heparin		20.6	20.0

followup revealed no significant differences between treatment groups in angiographic scores and pulmonary arterial pressures.

In an attempt to decrease costs and lower hemorrhagic complications, Edwards treated nine consecutive patients suffering massive embolism and shock with a low dose of urokinase (200,000-300,000) infused over two hours followed by heparin 10,000 U IV q4h.[20] The urokinase was infused directly into the pulmonary artery and provided rapid clinical improvement with clot lysis and no hemorrhage. Six of the nine patients had recurring pulmonary embolism, however, with death resulting in two.

Through a retrospective review of 68 patients with acute pulmonary embolism, Miller et al. evaluated the rate of treatment failures and mortality in shock versus nonshock patients treated with heparin, streptokinase, or embolectomy as primary therapy.[21] The observation was made that when heparin was used as primary therapy, there were a greater number of total deaths and failures (50%) than with either streptokinase or embolectomy (25%).

In a controlled trial by Ly et al, patients with major pulmonary embolism were allocated randomly to receive streptokinase or heparin.[22] The angiographic evidence of thrombolysis was significantly greater in the streptokinase group ($P < 0.01$). Two deaths were reported in the heparin group, one from massive embolism 15 hours after the start of treatment and the other four weeks later from a cerebral glioblastoma. In the streptokinase group, one patient died from a thrombotic occlusion of the inferior vena cava three weeks after treatment.

A summary of the major clinical trials utilizing urokinase, streptokinase, and heparin for pulmonary embolism appears in table 1.

Deep Vein Thrombosis

The rapid lysis of thrombi in the deep veins by streptokinase tends to preserve the anatomy and function of the venous valve cusps, whereas the slow resolution of thrombi with heparin therapy seems to permit distortion and destruction of the valves.[23] In the studies reviewed, streptokinase was generally used in the recommended doses for 72 hours in patients with less than two weeks' duration of symptoms. Venography was used in most cases to assess the decrease in blood flow due to emboli and to observe the results of heparin or thrombolytic therapy. Analysis of study results revealed that thrombolysis was significantly greater with streptokinase, with complete lysis occurring in 30% of patients and substantial lysis in 65%.[24-29] Patients receiving heparin therapy experienced less than a 10% lysis.[24-29] The incidence of pulmonary embolism was approximately the same for both groups.[24, 26-28, 30]

Seaman et al studied 50 patients and found that the degree of thrombolysis was significantly greater in the streptokinase-treated patients than in the heparin-treated patients ($P < 0.05$) after three days, although after ten days the difference decreased to a non-significant level.[31] Common et al observed that in patients with more extensive disease, when either heparin or streptokinase is started later than the third day of onset, the usual result is healing by recanalization without valve preservation. Both Dhall et al and Tsapogas et al suggested that successful therapy correlated with initially low fibrinogen levels and substantially decreased levels after 24 hours.[25, 30] Duckert et al and Watz et al noted that thrombolytic therapy was most effective when the thrombosis was located in the proximal rather than in the calf veins.[27, 28]

The incidence of post-thrombotic syndrome was also examined in several studies. Common et al evaluated patients with similar distributions of clot severity after a mean of seven months.[23] Normal venograms were found in 40% of the streptokinase group but only 8% of the heparin group. In a study by Elliott et al, only one of the 17 patients who achieved 80-100% lysis with streptokinase developed postphlebitic symptoms, whereas only two of the 25 patients treated with heparin were found to have asymptomatic legs on followup.[26] No significant lysis was achieved in any of the 25 patients treated with heparin.

A summary of the major clinical trials using streptokinase and heparin in deep vein thrombosis appears in table 2.

Arterial Thrombosis and Embolism

In a small number of studies, streptokinase has been used successfully in the treatment of acute arterial thrombi and emboli. In 1974, Dotter et al reported their development of a selective-delivery, low-dose technique that concentrated the therapeutic action of streptokinase where it was needed.[49] In their series of 17 patients, indwelling selective catheters were used to perfuse streptokinase just above or

Table 2.
Summary of Clinical Trials Utilizing Streptokinase and Heparin in Deep Vein Thrombosis

Reference/Study Design	Number of Patients	Drug	Venography (%)	Morbidity (%)
Common et al[23] randomized, follow-up	27	Streptokinase	(at mean, seven months) normal venogram(40) segmental venogram (6) complete recanalization (26) partial recanalization (26)	swelling (33)
		Heparin	normal venogram (8) segmental venogram (8) complete recanalization (58) partial recanalization (26)	swelling (50)
Elliott et al[26] controlled, randomized	51	Streptokinase	80-100% (74) partial lysis (9)	(0)
		Heparin	no significant lysis (8) extension of thrombosis (8)	(8)
Duckett et al[27] controlled, nonrandomized	145	Streptokinase	complete lysis (42) partial lysis (25)	pulmonary embolism (7.5)
		Heparin	complete lysis (0) partial lysis (10)	pulmonary embolism (12)
Watz et al[28]	35	Streptokinase	at 24 hrs-complete lysis (44)	high valvular function (91)
			at 1-2 months-complete or partial lysis (66)	
		Heparin	at 24 hrs-complete lysis (6)	high valvular function (13)
			at 1-2 months-complete or partial lysis (35)	
Tsapogas et al[30] controlled, randomized	34	Streptokinase	complete or partial lysis (53)	(0)
		Heparin	complete or partial lysis (9)	pulmonary embolism (9)

directly into obstructing intra-arterial thromboemboli. Fresh clots readily dissolved with doses as low as 1/100th of those given intravenously to cause a therapeutic systemic hyperlytic state. A marked concomitant reduction in distant bleeding was also achieved.

While conducting a prospective, randomized, single-blind comparison of streptokinase with heparin therapy in 17 patients, Reichle et al found that total limb salvage was possible in 72% of the patients who received streptokinase compared with only 33% of the patients treated with heparin.[32]

In another prospective, uncontrolled study conducted by Martin and involving 600 patients, streptokinase produced a clearance of femoral and ileac occlusions in 75% of the patients with symptoms of less than two weeks duration.[33] The reocclusion rates of ileac arteries averaged from 0-12%, however, while the femoral artery reocclusion rate approximated 50% at the end of the third year.

Totty et al investigated the use of low-dose fibrinolytic agents administered via an indwelling angiographic catheter in 22 patients with intravascular thrombi.[50] Thirteen perfusions were performed in association with 10 percutaneous transluminal angioplasty procedures. Of these, eight produced complete or nearly complete lysis of radiographically visible thrombi, while five brought about only partial lysis. Thirteen infusions were also performed in 12 patients who presented with acute or subacute vascular thrombosis and were not considered candidates for angioplasty. Partial lysis was seen in all but one of the patients with spontaneous thrombosis; however, no patient had complete lysis.

In a recent study conducted by Berni et al, successful thrombolysis was achieved in 12 of 16 arterial occlusions (75%) following intra-arterial infusion of streptokinase at a dosage of 5,000 U per hour.[51] All 16 of the occlusions were classified as being acute on the basis of a sudden development of ischemic symptoms within two weeks before the initiation of therapy. The incidence of successful lysis was similar in embolic occlusions (80%) and thrombotic occlusions (70%). The time interval from the onset of symptoms to the initiation of treatment ranged from 2 hours to 10 days, which approximates the age of the clot or thrombus. Lysis occurred in 78% of the occlusions treated within 24 hours compared with 71% in those of longer duration. Therefore, neither the etiology nor the duration of the occlusion influenced the ability to achieve effective thrombolysis.

Low-dose intra-arterial streptokinase therapy appears to be an effective alternative in the treatment of thromboemboli producing acute arterial occlusion. The major limitations of thrombolytic therapy are the time interval required to ensure complete thrombolysis and preserve the viability of the limb. Although low-dose intra-arterial streptokinase appears to be associated with a decrease in the incidence of hemorrhagic complications, hypofibrinogenemia and bleeding abnormalities continue to be a problem.

Acute Myocardial Infarction

Several multicenter studies have used intravenous streptokinase in the treatment of acute myocardial infarction. The rationale was that the size of the infarct might be reduced by prevention of thrombosis in small vessels at the periphery of the infarct. Controlled trials in both the United Kingdom and Australia evaluated several hundred patients but were unable to demonstrate a significant decrease in mortality compared with placebo or other anticoagulants.[34, 35] However, patients were entered into these trials up to 72 hours following the onset of symptoms. In the European cooperative trial, a decrease in mortality from 30.6% to 15.6% within six months was demonstrated with streptokinase compared with placebo when initiation of therapy took place within 12 hours of onset of symptoms. Only 13.5% of all patients with myocardial infarction, however, were included in the study.[36]

Stampfer et al evaluated the efficacy of intravenous streptokinase in reducing mortality after acute myocardial infarction by pooling results of eight randomized clinical trials from 1969 to 1979.[37] Statistical analysis of results suggested that therapy with intravenous streptokinase after myocardial infarction reduced mortality by approximately 20% over the subsequent few weeks, with a protective effect suggested beyond the sixth week.

Spann et al reviewed the literature on the use of intravenous streptokinase in myocardial infarction and reported their experience with high-dose intravenous therapy in 13 patients under the age of 70 years with transmural myocardial infarction and duration of symptoms of less than six hours.[38] Streptokinase 850,000 IU IV was administered over one hour. Clot lysis and angiographically demonstrated coronary reperfusion were reported in six of these patients within one hour of starting the infusion in this ongoing study. Their review of the literature had indicated that successful recanalization after intravenous therapy has been reported in 45-65% of patients, as compared with 75% who received intracoronary infusion.

Encouraged by findings that thrombus formation is a frequent cause of total coronary occlusion in the early hours of myocardial infarction, several investigators have used streptokinase for intracoronary thrombolysis. Jerome Weinstein analyzed efficacy and safety data from 209 U.S. cases in the Hoechst-Roussel intracoronary streptokinase registry.[39] Successful recanalization was achieved in 76% of infarct-related occluded coronary arteries. Among the 209 cases, 14 adverse reactions associated with the use of streptokinase were reported. There were six cases of excessive bleeding or hematoma reported at the site of the insertion. Since all patients with bleeding problems were already heparinized, however, it is unclear to what extent streptokinase contributed to this complication.

In a study by Reduto et al, coronary angiography was performed on hospital admission in 32 consecutive patients with acute myocardial infarction.[40] Twenty-six patients had total occlusion of an infarct-related coronary artery. In 18 of these patients, intracoronary infusion of streptokinase resulted in reperfusion of the distal coronary artery. Hemodynamic indexes of left ventricular performance and ejection fraction did not change immediately after reperfusion. The mean left ventricular ejection fraction increased significantly ($P = 0.007$) from hospital admission to discharge in patients exhibiting reperfusion of the occluded coronary artery.

Markis et al evaluated intracoronary streptokinase 2.3-4.3 hours after the onset of symptoms in nine patients with acute myocardial infarction.[41] Occluded coronary arteries were opened in all patients, but reocclusion occurred in one patient. Improved regional perfusion was observed in seven of nine patients.

Despite limited data, thrombolysis with streptokinase, either by intracoronary or intravenous administration, appears promising in the treatment of acute myocardial infarction. Although coronary thrombolysis appears to occur more frequently with the intracoronary route of administration, the intravenous route will enable treatment of a larger number of patients. In addition, streptokinase can be administered earlier by the intravenous rather than the intracoronary route due to its simplicity. This is important, since coronary thrombolysis can be achieved much more quickly and effectively when the drug is administered early.[34-41] The sooner reperfusion of the coronary artery is achieved with streptokinase, the greater the chances of salvaging the jeopardized myocardium.

Arteriovenous Cannula Occlusion

Streptokinase has been used for clearing of totally or partially occluded arteriovenous cannulae.[15] Rethrombosis of these shunts, however, may occur at a variable interval.[11]

Miscellaneous Uses

Thrombolytic agents have also been investigated in numerous other clinical situations. Streptokinase has been used in obstruction of the bronchus by clots, retinal vein thrombosis, heart valve obstruction, obstruction of the peritoneal dialysis catheter, and hemothorax.[42-46] Urokinase has been used in cerebral infarction and renal-cortical necrosis.[47, 48]

Dosage and Administration

Streptokinase is available as Streptase from Hoechst-Roussel Pharmaceuticals and as Kabikinase from Kabi Group. Streptase is supplied as a lyophilized white powder in vials containing 250,000 and 750,000 IU of purified streptokinase. Kabikinase is available in 5 ml vials containing 250,000, 600,000 and 750,000 IU per vial of purified streptokinase. A loading dose of streptokinase is required to neutralize streptococcal antibodies present in the circulation. In the United States, a loading dose of 250,000 IU, administered intravenously over 30 minutes, has been found to be appropriate in approximately 90% of patients.[15] A maintenance dose of 100,000 IU/hour for 12-72 hours follows the loading dose. Although the optimal duration of therapy has not yet been established, streptokinase is usually given for 24 hours to patients with pulmonary embolism, and for 72 hours for deep vein thrombosis.[15] When administered via the intracoronary route, a bolus dose averaging 20,000 IU and a maintenance dose averaging 2,000 IU/min for 60 minutes has resulted in opening of occlusions within one hour in greater than 75% of patients. The duration of

therapy for acute myocardial infarction varies from 12-72 hours in most studies.[34-41] In most patients the thrombin time will be prolonged two to five times the normal control value. If the thrombin time after four hours of therapy is less than 1½ times the normal control value, therapy should be discontinued because of the possibility of excessive resistance due to high streptococcal antibody titers from a recent streptococcal infection.[11, 15-17]

Urokinase is available as Abbokinase from Abbott Laboratories and Breokinase from Breon Labs. Both are supplied as a sterile lyophilized preparation. Each vial contains 250,000 IU urokinase activity. A priming dose of urokinase 4400 IU/kg, dissolved in normal saline, is administered over a period of 10 minutes. This is followed by a continuous infusion of 4400 IU/kg/hour for 12 hours. The total volume of fluid administered should not exceed 200 ml.[14]

Following thrombolytic therapy with either drug, treatment with heparin by continuous infusion without an initial bolus is recommended. Heparin treatment should not begin, however, until the thrombin time has decreased to less than twice the normal value.

Adverse Effects

Bleeding. The incidence of major bleeding has been reported to be about 5-20% with streptokinase and urokinase.[17, 22, 27] Minor bleeding secondary to venous cutdowns and other causes has been reported to be about 20% with thrombolytic agents.[14, 15]

In cases of serious bleeding, streptokinase therapy must be discontinued and plasma administered. If very rapid reversal of the fibrinolytic state is required, treatment with aminocaproic acid can be instituted.[11, 15] Aminocaproic acid inhibits activation of plasminogen by streptokinase and is usually given in a dose of 5 g during the first hour, followed by a continuous infusion of 1 g/hour until the hemorrhagic condition is under control.[11]

Hypersensitivity Reactions. Hypersensitivity reactions associated with streptokinase include urticaria, itching, flushing, nausea, headache (12%), transient elevation or decrease of systolic blood pressure of greater than 25 mm Hg (2%), and anaphylaxis (1.3-2.5%).[15, 17, 28]

Although urokinase is a protein of human origin, *in vitro* and *in vivo* tests have shown no evidence of inducing antibody formation. The possibility of serious allergic reactions cannot be excluded.

Fever. With streptokinase use, the incidence of temperature elevation greater than 1.5°F is 30%, but only 3.5% have temperatures in excess of 104°F.[17, 22, 27, 30] Febrile episodes with urokinase have occurred in approximately 15% of patients.[17]

Phlebitis. The incidence of phlebitis at the infusion site is about 2%, and further dilution of streptokinase helps alleviate this problem.[15]

Summary and Conclusion

All the studies reviewed agree that thrombolytic agents are superior to heparin alone in accelerating the lysis of pulmonary thromboemboli, restoring normal pulmonary circulation, and decreasing elevated right heart pressures. No significant differences, however, in overall morbidity and mortality have been noted between most heparin-treated and streptokinase-treated patients. In patients with massive pulmonary embolism and shock, several studies have shown a significantly higher recovery rate with thrombolytic agents if used within the first 72 hours after onset of symptoms.[16-22]

Streptokinase was also found to be more effective than heparin in the lysis of extensive ileo-femoral thrombi if used within seven days from the onset of symptoms.[23]

The use of streptokinase in the treatment of acute myocardial infarction appears promising, with coronary thrombolysis occurring more frequently when the drug is administered via the intracoronary route. Further studies are necessary to determine whether long-term morbidity and mortality are decreased.

In conclusion, the use of streptokinase should be limited to patients with massive pulmonary embolism with shock, proximal deep vein thrombosis, and arteriovenous cannula occlusion. The use of regional streptokinase in acute myocardial infarction seems promising, although this therapy should be reserved for those patients refractory to the more conventional types of treatment. Although the approved indications for urokinase are limited to pulmonary embolism and arteriovenous cannula occlusion, the therapeutic and toxic differences between it and streptokinase appear to be insignificant. Since urokinase is much more expensive, streptokinase should be considered the thrombolytic agent of choice.

NOTE: Complete bibliography is available through the office of the North Carolina Medical Journal, Box 3910 Duke Hospital, Durham 27710.

Price per vial

Streptokinase	
Kabikinase	*Streptase*
250,000 IU — $33.75	250,000 IU — $42.24
600,000 IU — $63.75	750,000 IU — $93.24
Urokinase	
Abbokinase	
250,000 IU — $154.38	

Premarital Legal Requirements

Louise H. Poe, MT (ASCP), MPH

THIS article is designed to eliminate some of the confusion that surrounds the physical examination and laboratory tests required for a marriage license. Requirements vary among states and are subject to frequent changes. The following general information concerns both in-state and out-of-state premarital requirements.

North Carolina Requirements

North Carolina *does not* have a statute that requires a premarital laboratory test of any kind. North Carolina does have a requirement (G.S. 51-9) that a health certificate be presented to the Registrar of Deeds when securing a marriage license. This certificate (Division of Health Services [DHS] No. 1836) must be signed and dated by a licensed physician. It is left to the discretion of the examining physician to decide by the "usual means of examination" if the applicant meets the "requirements" set forth in G.S. 51-9. These requirements are found on the back of DHS 1836.

Out-of-State Requirements

Persons planning to be married in another state must satisfy the requirements of the state in which the marriage is to be performed. These requirements may include performance of laboratory tests in approved laboratories. Most states will accept laboratory test results in the following facilities:

- State health laboratories
- Hospitals accredited by the Joint Commission on Accreditation of Hospitals
- Hospitals otherwise approved to participate in the Medicare program
- Federal laboratories (Veterans Administration, Public Health Service Hospitals and military hospitals and/or institutions)
- Independent laboratories that participate in the Medicare and/or Clinical Laboratory Improvement Act program.

A few states will not accept any laboratory test results from an out-of-state laboratory. A few states have no requirements for premarital laboratory tests or examinations.

Other Approved Laboratories

Although the North Carolina law requiring premarital syphilis serology testing has been repealed, there is a law that requires a test for prenatal syphilis serology. The Department of Human Resources, Division of Facility Services approves laboratories for this purpose. They may be found in hospitals, health departments or other facilities such as clinics and physicians' offices. If other states require a premarital syphilis test, they will usually accept test results from laboratories that are approved by the Department of Human Resources for prenatal syphilis serology to satisfy this requirement.

Branch Laboratories

Some states have branches of their state health laboratories; test results are usually accepted from these branches for marriage licenses. Even though the North Carolina Division of Health Services Laboratory Section does not have branches, county health department laboratories come under the state's certification program (for prenatal syphilis serology only) and would, therefore, be acceptable to most other states for premarital syphilis serology testing.

Authorized Persons

Out-of-state premarital application forms may have a laboratory result section requiring the signature of an "authorized person" (i.e., an official of the North Carolina Department of Human Resources). Should this be the case, the form may be mailed to the Chief, Licensure and Certification Section, Division of Facility Services, Department of Human Resources, P.O. Box 12200, Raleigh 27605-2200. This individual has the authority to certify that a laboratory is approved (licensed and/or certified). After signing, the Chief of the Licensure and Certification Section will return the form to the physician or laboratory. If the test is performed in the North Carolina Division of Health Services Laboratory the technologist who performed the test may sign the form.

Requirements for Licensed Physicians

The requirement that a licensed physician perform the premarital examination varies among states. Some states require that the physician be licensed in the state where the marriage is to be performed. Other states will accept a physical examination performed by a physician licensed in another state. North Carolina will accept documentation from any licensed physician in any state or territory of the United States, the District of Columbia or Puerto Rico. Most states will accept the premarital examination from a medical officer of the armed forces or Public Health Service, even though he may be licensed in another state and is temporarily on a tour of duty.

Acceptable Premarital Forms

Some states will not accept any form or premarital ex-

From the Licensure Unit, Division of Facility Services, Department of Human Resources, Raleigh 27605.

aminations except their own. It is advisable to obtain information about requirements and required forms from the State Health Department or local Registrar of Deeds where the marriage will occur. Out-of-state forms may be obtained for most states from the North Carolina Division of Health Services Laboratory. North Carolina will accept an out-of-state form if the other state has a comparable law.

Marriage License Requirements

North Carolina does require a marriage license. General Statute 51-6 states that marriage without a license is unlawful and that no minister or officer shall perform a ceremony of marriage until a marriage license is delivered to him signed by the Registrar of Deeds in the county in which the marriage is intended to take place.

Age Limits and Other Requirements

Each state has different requirements for obtaining a marriage license. These may include age limits ranging from 13 to 21, with different ages applying to men and women. In some states a woman may obtain a marriage consent if she is pregnant although she may be under age. In other states consent may require a court order, consent of one or both parents, consent of a probate judge or combination of a host of other requirements. In North Carolina the legal minimum age for marriage is 18 for both men and women and consent is required if the marriage applicants are younger.

Summary

Agencies in North Carolina that will assist the physician and marriage applicants in meeting the premarital syphilis serology testing requirements of another state are:

For out-of-state forms
North Carolina State Laboratory of Public Health
Virology/Serology Branch
P.O. Box 28047
Raleigh, NC 27611
Telephone: 919/733-7544

Health Certificate (DHS-1836)
Division of Health Services
Mailing Unit
P.O. Box 2091
Raleigh, NC 27602
Telephone: 919/733-7206

Laboratory Certification Program
Division of Facility Services
Licensure and Certification Section
Licensure Unit
P.O. Box 12200
Raleigh, NC 27605
Telephone: 919/733-2786

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An Update on Physician Assistants: The N.C.A.P.A. Survey

Wayne W. VonSeggen, PA-C and John F. Bolles, PA-C

DURING 1982 the North Carolina Academy of Physician Assistants, with the encouragement of the Committee on Allied Health Professionals of the North Carolina Medical Society, prepared an 80-question survey and sent it to the 406 physician assistants (PAs) registered to practice in North Carolina. The return rate was 60% (244/406). The purpose of this 1982 survey was to gather information to assess the following general areas:

What are the current demographic statistics on physician assistants in North Carolina?

What are characteristics of the medical practices where physician assistants are employed?

What are the current salaries, compensations and benefits among North Carolina physician assistants?

How are physician assistants being supervised by their employing physicians?

What do physician assistants feel about several issues that are facing them?

General Demographic Information

The average age of all North Carolina PAs is 33.4. The average male age is 34 years, and 70% are male. The average female age is 32 years. The fact that 30% of practicing PAs are female indicates a significant change in the pool of individuals entering this profession. Early studies showed nearly complete male preponderance since the individuals initially being trained as PAs had military medical corpsman experience. In recent years, some PA programs in N.C. have been training classes composed of up to 50% females.

Ninety-one percent of practicing PAs are Caucasian and 6.6% are Afro-American; 0.4% are "other" races, and 2.0% chose not to answer.

The average number of years of health care experience prior to entering the PA profession is 4.7 years. Some PAs have had up to 10 years prior health care experience.

Eighty-nine percent are graduates of a 24-month PA training program. Six percent have had formal PA training longer than 2 years. Only 4% have had training of between 1 and 2 years. No PA in N.C. has had less than 1 year of formal training.

Ninety-one percent of PAs in North Carolina have passed the certifying exam by the National Commission on Certification of Physician Assistants (NCCPA). Since at the time of survey the N.C. Board of Medical Examiners required all new PAs to pass this exam before being registered, the other 9% probably represent the number of PAs who were "grandfathered" under provisions of the NCAC 32D.0003(3): "Applicants who have graduated prior to December 31, 1980 shall be exempt from NCCPA certification."

Membership in physician assistant organizations has increased in recent years. Now 53.4% of North Carolina PAs responding to this survey are members of the American Academy of Physician Assistants. Approximately 50% of all PAs in the United States are members of the AAPA to date.

The average length of time in practice in this survey is about 5 years; the range is 6 months to 11½ years. Forty-five percent (111) have had only one job since becoming a PA; 35% (86) have had two different (successive) employers as a PA; 19% have had three or more jobs since beginning PA practice.

Practice Information

The PAs were asked to indicate the general type of practice in which they are employed:

24% (59) — Family Practice
14% (34) — Internal Medicine
10.7% (26) — Emergency Medicine
18.5% (45) — Surgery
32.5% (79) — Other

Over 60% of these "other" practices included Psychiatry, Pediatrics, Health Clinics, Occupational Medicine, OB-Gyn, Alcohol Treatment-Detoxification Clinics, and Rehabilitation Medicine.

The PAs described their present practice employer as follows:

22% (54) work with a solo M.D.
6.8% (16) work with a two-M.D. partnership.
24% (57) work with a group practice.
27.4% (65) are employed by M.D.'s at a hospital.
19% (45) are employed in other situations, such as an HMO, a corporation, university, or other organization.

The PAs were asked to give the number of physicians who have a part in their supervision. The results are:

32.2% (77) have one supervising physician.
24.6% (59) have two supervising physicians.
11.7% (28) have three supervising physicians.

This survey was supported by North Carolina Academy of Physician Assistants.

9.2% (22) have four supervising physicians.
17.1% (41) have five to nine supervising physicians.
5% (12) have 10 or more supervising physicians.

(Note: All PAs have one primary supervising physician regardless of the number of backup supervising physicians.)

The PAs were requested to give the number of other PAs in their practice:

58% (138) are the only PA in their practice.
19% (45) work with one other PA.
23% (56) work with more than one other PA in their practice.

Twenty-six percent of the PAs describe their practice setting as being located in a medically underserved area.

By population of their practice area, 28% say they are employed in an area of less than 15,000. Another 24% work in an area with a population of between 15,000 and 50,000.

There is wide variation in the scheduled hours to work and wide variations in on-call responsibilities among PAs. The average scheduled working hours for a PA are probably 45-50 hours per week.

Office vs. Hospital Practice

The PAs were questioned about the percentage of their time they spend working in an office/clinic setting or in a hospital setting. Their responses follow:

Percent of working time	*Office/clinic setting*	*Hospital setting*
0	28.5%	27 %
25	55	21.7
33	4.6	5.3
50	9.4	8.2
66	6.8	3.7
75	17.8	4.1
100	27.2	30

Hospital Privileges

In this study, 13.3% of the PAs say that hospital privileges are *not* required in their present work setting; 190 (79%) have hospital privileges. In a related question, 178 PAs in this survey said that they worked some part of their day in a hospital. It is possible that some PAs may have been in the process of gaining hospital privileges since 8 of 18 PAs without hospital privileges have been in practice less than 2 full years. For those (5) who do not have hospital privileges and who have been in PA practice over 5 years, only one has had two different employing practices. The other 4 PAs are still in their initial employing practice, indicating either satisfaction with the arrangement or resignation to the situation.

Job Description

62% consider their position "mostly primary care." When asked to describe the major responsibilities of their job, these were their responses:

Clinical 96.3% (235)
Administration 2.5% (6)
Teaching 0.8% (2)
Research 0.5% (1)

The source of funding for the present job of the PAs was given as:

Private 52.0% (123)
State 19.5% (46)
Federal 7.6% (18)
Corporation 16.5% (39)
Other 3.8% (9)

Only 21% of the PAs have actually signed a written contract, but 80% would recommend a written contract for a PA.

The types of practice PAs are now working in are:

Family Practice/Family Medicine 24.3% (59)
Internal Medicine 14.0% (34)
(includes Cardiology, Gastroenterology, Hematology, Oncology, Nephrology, Pulmonary, Allergy, Critical Care, Rheumatology)
Emergency Medicine 10.7% (26)
Surgery 18.5% (45)
(includes Orthopedics, Plastics (Burn Center), General, ENT, Neurosurgery, Ortho-Hand, Urologic, Vascular)
Other 32.5% (79)
(includes Psychiatry, Pediatrics, Health Clinic, Occupational Medicine, OB-Gyn, Alcohol Treatment-Detoxification Clinic, Rehabilitation, 4 each; Cardiology, Computer Research, Dermatology, Family Practice and E.R., Geriatrics, Hematology, Hospital Admissions, Institutional, Neurology, Ophthalmology, Planned Parenthood, Rural Health Clinic, University Student Health Clinic, Urology, VA (unspecified), Correctional, Pediatric Hematology-Oncology)

Compensation and Benefits of PAs

The average base salary per year (not including fringe benefits) for all PAs answering this part of the survey (N = 234) was $22,436. The average for male PAs was $23,311, for female PAs $20,491.

The gender averages may not be as dependent upon gender as they are upon the fact that in the earlier years of PA training the pool of applicants for PA programs was ex-military corpsmen. These males would tend to have higher salaries now simply because they have been in practice longer.

Table 1 lists the salaries and length of time as a PA. Table 2 lists salaries and years in present position as a PA. Table 3 lists salary averages in different types of practice.

The average percent increase in the base salary per year since accepting their present job was 10.7%. The average number of sick days allotted per year was 10.7 days; about 9% have no specified maximum number but use what they need. The average number of vacation days allotted per year is 14, with a range of zero to 36 days.

The following benefits table was presented to the PAs in the survey. The number at the left represents the percentage of PAs in this survey who receive that benefit.

54% Life insurance at no charge
27% Life insurance at a group rate

Table 1
Salary vs. Years as P.A.

Years as P.A.	Average Salary	Range	
Less than one year (N = 3)	$16,167	$16,000	$16,500
One year (N = 6)	18,091	16,200	19,600
Two years (N = 32)	19,833	15,000	28,000
Three years (N = 35)	21,002	16,000	27,500
Four years (N = 42)	23,298	16,000	33,960
Five years (N = 28)	22,805	17,000	28,000
Six years (N = 22)	26,057	18,000	38,000
Seven years (N = 9)	26,167	21,000	34,000
Eight years (N = 19)	25,899	16,000	31,200
Nine years (N = 16)	28,268	19,200	40,000
Ten years (N = 14)	25,771	18,000	32,000
Over ten years (N = 6)	24,983	18,000	29,700

Table 2
Salary vs. Years in Present Position as P.A.

Years in Present Position	Average Salary	Range	
Less than one year (N = 11)	$18,163	$16,000	$22,400
One year (N = 39)	20,713	16,200	40,000
Two years (N = 51)	20,363	15,000	28,000
Three years (N = 34)	22,627	16,000	35,000
Four years (N = 25)	22,218	18,000	33,960
Five years (N = 20)	24,874	16,000	31,290
Six years (N = 16)	25,116	19,000	38,000
Seven years (N = 16)	25,584	20,000	31,200
Eight years (N = 4)	27,500	24,000	32,000
Nine years (N = 7)	24,586	18,000	30,000
Ten years (N = 5)	24,040	22,000	26,700
Over ten years (N = 2)	21,750	18,000	25,500

Table 3
Salary Averages for Different Types of Practices

Type of Practice	Number of Respondents	Average Salary
Family Practice	59	$22,457.27
Internal Medicine	34	$22,758.73
Emergency Medicine	26	$23,076.00
Surgery	45	$23,195.61
Other	79	$21,617.71

53% Personal health insurance at no charge
25% Personal health insurance at reduced charge
16% Family health insurance at no charge
39% Family health insurance at reduced charge
50% Disability insurance paid by employer
22% Profit sharing
78% Allotment for continuing medical education paid by employer. (Average of $641/year for those who filled in a designated amount for CME.)
43% Professional organization fees paid by employer
46% Recertification fees (NCCPA) paid by employer
86% Malpractice coverage provided at employer's expense
53% Pension plan or IRA or long-term investments provided
90% time off to attend CME events
81% Do not have to use vacation time when attending CME events, paid as if they were working in their own practice

Supervision of Physician Assistants

PAs are trained to work as dependent physician extenders providing health care services under the supervision of a physician. Each registered PA in North Carolina must by definition have a primary supervising physician, registered with the N.C. Board of Medical Examiners (NCBME), who is ultimately responsible for the actions and services provided by the PA under that physician's supervision. Many PAs work in group practices, where they have a single supervising physician and one or more backup supervising physicians.

The average number of supervising physicians for the PAs in this survey is 3.4 physicians per PA. Here is a further analysis:

31.5% (76/241) have a single supervising physician
24.0% (58/241) have two supervising physicians (one primary and one backup)
11.6% (28/241) have three supervising physicians
9.1% (22/241) have four supervising physicians
22.0% (53/241) have five or more supervising physicians

A majority (55.5%) of PAs in North Carolina are supervised by solo or two-physician practices. Only 11 PAs (4.5%) listed 10 or more physicians who have a part in their supervision. Many PAs have one or two physicians with whom they interact daily and are supervised by, but may in fact have several backup physicians to be available when the primary physician is unavailable, such as during illness, medical meetings, days off, or vacations.

Of the PAs surveyed, 94.4% are satisfied with the degree of supervision by their physicians; 92% feel that the relationship with their supervising physician is "satisfactory."

There are a variety of methods of supervising a PA including actual physical presence of the physician, chart review by the physician, telephone consultations, and time-saving written standing orders for the PAs. Standing orders are standardized treatment protocols for typical problems encountered in their practice.

Sixty percent of PAs have their supervising physician physically on site all the time. Another 18% say their supervising physician is on site where they are working 50% of the time. Another 12% say their supervising physician is on site less than 50%, while only 3% say their supervising physician is on site one day per week. (Note: For those times when the physician is not on site, other methods are available for the PA to consult the physician, or chart review is being done.)

Daily chart review of the PA is a method of supervision used by 54% of supervising physicians, in addition to other methods. *Weekly* chart review is used by 10%. *Sporadic* chart review is used by 10% of the supervising physicians. Phone consultation in some manner between the PA and the physician is used by 33% of the practices. Of those who have weekly chart review or sporadic chart review, 84% have their supervising physician on site all the time. There were no PAs in this survey who gave "sporadic chart review" or "phone consultation" as their only method of supervision.

The only type of supervision that concerned the authors was "M.D. on site one day per week" plus "weekly chart review by M.D." This combination of supervision seems to be less than the recommendations set by the NCBME. The other 99.5% of PAs listed various combinations of physician supervision that would seem to insure adequate PA supervision by a physician.

Many practices make use of written standing orders. About 10% of the practices do not use written standing orders because the physician is on site 100% of the time. About 80% of the practices in this survey either have standing orders or are currently developing standing orders. Another 9.4% do not use standing orders as part of their methods of PA supervision.

For those who have written standing orders, 24% are using "Patient Care Guidelines for FNPs" by Hoole, Pickard, and Greenburg; 36% developed their own set of standing orders; 34.7% are using a combination of the two; and 4.7% are using other prepared standing orders such as the "Washington Manual," or other printed clinical protocols.

Issues Facing Physician Assistants in North Carolina

At the time this survey was taken in 1982, the NCBME required each PA in the state to have passed the national certification examination for primary care physician assistants by the NCCPA (National Commission on Certification of Physician Assistants). Several of the questions on the survey dealt with PAs' attitudes about NCCPA certification.

On the survey, 38.6% felt that passing the NCCPA exam should be a mandatory requirement for PA registration. (Note: On July 1, 1983 the NCBME dropped NCCPA certification as a requirement for PA registration despite much testimony supporting the retention of the NCCPA exam as a part of registration in North Carolina.)

The PAs are fairly evenly divided in their view of the current Formulary for Physician Assistants, with 50.7% satisfied with the Formulary and 49.3% dissatisfied with it. For those who indicate dissatisfaction, the following general categories of suggestions for improvement were offered:

1. Clarify limitations on outpatient prescriptions vs. inpatient medication order writing.
2. It should be OK for PAs to write prescriptions for OTC medications.
3. Improve refill policy, especially for those patients not needing monthly reassessment.
4. Include approval for up to 3-month amounts of all antihypertensive medications and insulin.
5. Include approval for codeine in some limited form, either on a 24- or 48-hour limited prescription amount as an analgesic, or as part of Schedule IV or V (antidiarrheals and antitussives) in limited amounts.
6. Include tetracyclines, topical cleocin for acne, and chloromycetin ophthalmic preparations on a limited basis.
7. Expand refill authority for oral contraceptives.
8. Clarify the fact that additional authority to prescribe may be granted for specific situations upon request and subsequent approval by the NCBME.

On the survey, PAs were asked to rate the present employment opportunities for PAs in their area of North Carolina compared with three years ago. The results were:

9.4% — much better now than three years ago
21.4% — slightly better now than three years ago
33.5% — about the same as three years ago
23.7% — slightly worse than three years ago
12.1% — much worse now than three years ago

On another question regarding employment, the PAs were asked: "Have you been impeded from accepting or being considered for a specific job opportunity because of the BME's current policy of not registering PAs before NCCPA scores are received?" Of those to whom this policy applies, 9.2% (6/59) said they have been impeded by that policy. (Note: Since the NCBME has dropped NCCPA certification as a requirement for PA registration, there is no longer any "exam score delay" among recent graduates as far as registration is concerned.)

Of the PAs in this survey, 25% said that the lack of Medicare reimbursement for the services of PAs has been a problem in their personal practice.

The most definitive answer in the survey, about which the largest number of PAs agreed, came when they were asked whether they thought that the NCBME should have an advisory committee on PAs. A resounding 98.3% answered that the NCBME should have a formal advisory committee on PA matters. When given the opportunity to select their choice for the composition of such a committee, 70% chose a combination of PAs, supervising physicians, and representatives from PA training programs in North Carolina; 26% chose a combination of PAs and supervising physicians for such a committee; only 1% chose an option

that would have an advisory committee composed of physicians without PA representation.

Physician assistants are required to maintain 100 hours of continuing medical education every two years to retain membership in the national organization, the American Academy of Physician Assistants. The most popular ways to fulfill CME requirements are (in order of popularity):

76% CME sponsored by a local group
54% PA program-sponsored CME
47% Book and journal reading
44% NCAPA Conference
41% CME outside of North Carolina
36% Teaching
29% AAPA Conference
29% PA Journal (mailable CME exams)
15% Chart review
4% Research

At this time the number of PAs using CME sponsored by the N.C. Medical Society is negligible, even though PAs have been informally invited to participate. Of the PAs in this survey, 78% responded that their primary supervising physician is a member of the N.C. Medical Society. The PAs were asked: "If the opportunity presented itself, would you like to be an associate member of the N.C. Medical Society?" and a surprising 81% said "yes." It is possible that additional efforts by the N.C. Medical Society to include PAs in their CME activities could result in strong support among PAs seeking to acquire quality in-state CME.

The PAs were asked how they like being a PA. Ten percent chose "exceeds my expectations"; 17.5% chose "falls short of my expectations"; 66% chose "meets my expectations"; 6.1% chose "dissatisfied." No attempt was made to correlate dissatisfaction with those who said they are dissatisfied with their supervising physician or the quality of their supervision. However, 5.3% said they are not satisfied with the degree of supervision they have. No followup question was asked to determine whether the dissatisfaction might be caused by too little supervision, restrictive supervision, personality conflict, interprofessional problems, or purely deficient benefits.

We were interested in learning whether these PAs had at some time in their careers encountered active opposition to the PA profession. About 20% said they have experienced some opposition at some time. The most common source of opposition to the PA profession is from occasional nursing personnel and occasional hospital staff members. Despite occasional opposition, approximately half (48.9%) of the PAs said they would like to work a second job as a PA. In a followup question, 43.5% said they need another source of income to supplement their earnings from their current PA practice to meet their needs.

The job satisfaction among the PAs in this survey is evidently quite high, since 92.5% of the PAs indicated they intend to continue working as a PA for the next four years.

Summary

The physician assistant profession had its origins in North Carolina. The first PA training program started at Duke University in 1965. The American Academy of Physician Assistants was initially organized by North Carolina PAs. In this report, the current status of the PA profession in North Carolina has been described from information given in answers by PAs to an 80-question survey by the North Carolina Academy of Physician Assistants.

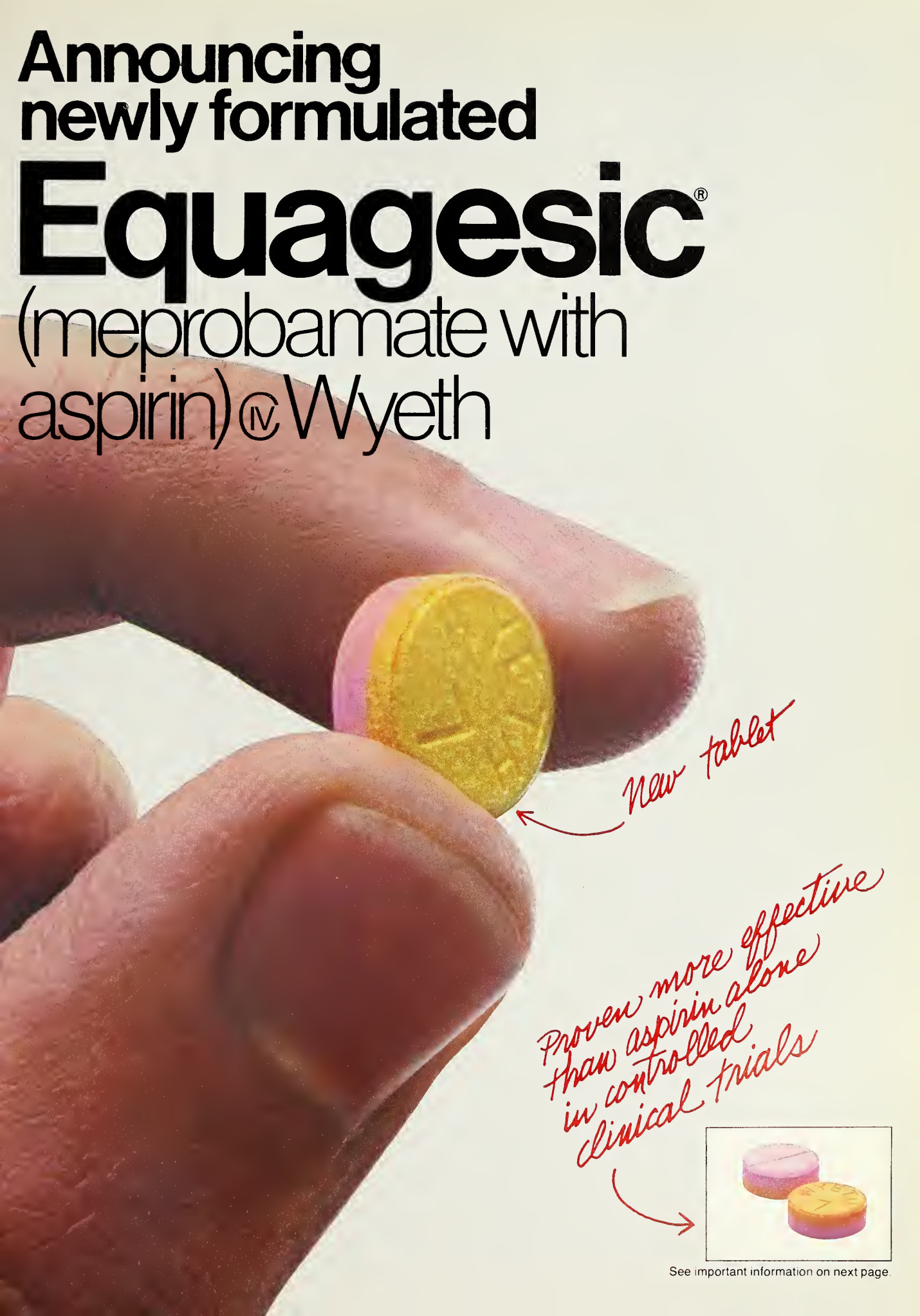
We hope this report will give North Carolina physicians an improved understanding of the physician assistant profession. For those physicians who currently do not employ a physician assistant in their practice, this report provides an overview of current salary, benefits, supervision methods, and attitudes of 60% of the PAs working in this state. Such information could be helpful to physicians seeking to remain competitive in the current medical marketplace where many efficient, active practices are utilizing PA services. For those physicians already supervising physician assistants, we hope this report will provide the basis for additional MD-PA interactions regarding improving supervision and upgrading benefits of the physician assistants on your health care team.

For more information on physician assistants please write to: North Carolina Academy of Physician Assistants, P.O. Box 27843, Raleigh, NC 27611.

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Effective adjunct in short-term treatment of pain
accompanied by tension and/or anxiety in patients with musculoskeletal disorders.



when anxiety magnifies the perception of pain



1-2 tablet dosage 3 or 4 times daily

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(BRIEF SUMMARY)

DESCRIPTION:
Each tablet contains 200 mg meprobamate and 325 mg aspirin

INDICATIONS:
Adjunct in short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease. Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone. Effectiveness in long-term use, i.e. over 4 months, has not been assessed by systematic clinical studies. Physicians should periodically reassess usefulness of drug for individual patients.

CONTRAINDICATIONS:
ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria, allergic or idiosyncratic reactions to meprobamate or related compounds, e.g. carisoprodol, mebutamate, or carbromal.

WARNINGS:
ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE: DRUG DEPENDENCE: Physical and psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually, greater than recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms, e.g. anxiety, anorexia, or insomnia, or withdrawal reactions, e.g., vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinosis, and, rarely, convulsive seizures. Such seizures are more likely in persons with CNS damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation, symptoms usually cease within next 12- to 48-hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e.g., driving or operating machinery.

ADDITIVE EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION:
An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physician about desirability of discontinuing the drug.

Meprobamate passes the placental barrier. It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS:
ASPIRIN: Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney, to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS:
ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS: Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity.

GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate/mebutamate and meprobamate/carbromal. Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC"): Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms.

DOSAGE AND ADMINISTRATION:
Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSAGE:
Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdosage produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole-blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal. The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported. Acute simple overdose (meprobamate alone): Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS:
0.5-2.0 mg percent represents usual blood-level range of meprobamate after therapeutic doses. The level may occasionally be as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdosage, such as stupor or light coma.

10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment. Some fatalities occur.

At levels greater than 20 mg percent, more fatalities than survivals can be expected.

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol): Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated. Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption.

HOW SUPPLIED:
Scored tablets, bottles of 100, Redipak® strip pack 25's, Redipak® unit dose 100's; individually wrapped.

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North Carolina Medical Journal

Features for Patients May 1984

The Patient Has a Sore Throat. What Should the Patient and Doctor Do?

Floyd W. Denny, M.D.

Upper respiratory infections, including sore throats, are the most common reason for visits to physicians in the United States.[1] The number of upper respiratory infections suffered by patients varies with age. During the first few years of life, children have 6 to 8 upper respiratory infections per year, depending on their exposure to older children and adults. This number decreases with each year of life; by school age the child will have 5 to 6 upper respiratory infections per year, and adults will have 3 to 4 per year.[2] Most of these infections are mild and require no medical attention, but a proportion are severe enough for the patient to seek medical care. This makes the problem of upper respiratory infections a major consideration in the delivery of medical care.

Viruses are the most common cause of upper respiratory infections and are thought to be responsible for over 85 to 90% of these illnesses.[2] Group A beta-hemolytic streptococcus (beta strep) has been considered for years the most important bacterium that causes upper respiratory infections. A recent study suggested that two other bacteria, *Mycoplasma pneumoniae* and *Chlamydia trachomatis*, may cause sore throats in adults, but this report is too preliminary to warrant any changes in the care of patients with upper respiratory infections.[3] Other bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, although important in such infections as pneumonia and otitis media (earaches), have not been shown to be important causes of upper respiratory infections. This means that the primary care physician is faced with the problem of deciding which of those patients with an upper respiratory infection has a viral infection for which there is no specific treatment and which has a streptococcus infection which can be treated with an antibiotic.

There are several reasons for treating patients with streptococcal upper respiratory infections (strep throat). The most important is that such treatment prevents the occurrence of rheumatic fever. Rheumatic fever that occurs after the symptoms of sore throat have subsided may affect the muscle or valves of the heart. Treatment also eradicates the streptococcus from the throat, thus preventing it from spreading to others or causing infections in other parts of the body, such as in sinuses, ears or lymph nodes. These complications occur in such a small number of patients that treatment just to prevent them is probably not warranted. Many people believe that treatment of strep throats results in rapid relief of symptoms, but controlled studies have shown that this is true only if the treatment is given very early during the infection (first 24 hours).[4] Even under this circumstance the time that the illness is shortened is limited because strep throats usually last only 3 to 5 days in patients who receive no treatment. Thus, the primary reason for treating strep throats in the past has been to prevent rheumatic fever.

At one time rheumatic fever was a very common and feared disease, but in the past few decades it has occurred so infrequently that many physicians rarely see cases. This apparent disappearance of rheumatic fever has presented several problems to physicians. Has rheumatic fever really gone away and if so, why? If rheumatic fever is no longer a problem, then how should the patient with a strep throat be managed in 1984? Patients are also faced with certain questions in this regard: When should they seek medical care for an upper respiratory infection or sore throat? Are sore throats a serious problem for them today? These complex issues were the impetus for a conference held in February 1983 and sponsored by Ross Laboratories,

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Illustrations by Ernest Croige, M.D.

the American Heart Assaciation and the Natianal Institute af Allergy and Infectiaus Diseases af the National Institutes af Health entitled "Management af Pharyngitis in an Era af Declining Rheumatic Fever."[5] This article summarizes my interpretation af the results af that canference, including the management af sare thraats in 1984.

Rheumatic Fever Is Disappearing in Developed Countries. Why?

Rheumatic fever is nat a disease that has ta be reparted, sa accurate figures an its accurrence are nat generally available. At the canference comprehensive studies from Baltimare and Memphis confirmed the widely-held impressian that the incidence of rheumatic fever has declined in the past few decades and is naw rarely seen by mast physicians. Since the canference, a repart fram Rhade Island hos confirmed the decline in that state.[6] The decline appears ta be true far industrialized cauntries, but rheumatic fever remains a significant problem in develaping cauntries.

Dr. Lean Gardis presented data which suggested that treating strep thraats is respansible, at least in part, far the decline in rheumatic fever. This abservatian is of great importance because the incidence af rheumatic fever appeared ta be declining *before* antibiatics were avoilable. The abservatian is alsa impartant because it dictates that we shauld cantinue ta treat strep throats ta prevent rheumatic fever. The big questian that remains far the physician in 1984 is whether the management af sare thraats shauld be changed in any way. Likewise, the patient ar the parent af the patient must decide whether ar nat a sare thraat requires a visit ta the dactor.



Ways to Diagnose Strep Throats

The physician has three sets af taals ta emplay in deciding which patients with a sare throat have a strep infectian: (1) the usual epidemialagical behaviar af strep infections, (2) the clinical manifestatians in the patient and (3) help fram the labaratary. Strep thraats are mast camman in children 5 ta 10 years ald and are unusual in children under 2 years af age and in the elderly. Their accurrence in adalescents and yaung adults is dictated primarily by situatians that increase cantact, such as schaals ar the military. Streptacaccal infectians have a definite seasanal preference for winter and spring. They are alsa assaciated clasely with crawding, and are seen more cammanly in such graups as schaal children and the paar. The classical symptams and signs af strep thraat are its abrupt anset, sare throat (pain an swallawing), fever, exudate (pus) an the tansils, tender and enlarged lymph nades in the neck and the accasianal rash af scarlet fever. Findings that suggest a diagnasis ather than strep thraat are a runny nase, caugh and vamiting and diarrhea (except in the yaung child). Unfartunotely, the clossic findings af strep thraat da nat accur in all infected patients; studies have shawn that twathirds ar less af cases can be diagnased accurately by these epidemialagical and clinical methads. Far the accurate diagnasis of strep throat help from the labaratary is essential.

A variety af labaratary tests has been used ta help diagnase strep thraats. Same af these are nonspecific, such as the number af white blaad cells or the erythracyte (red blaad cell) sedimentatian rate; nane has praved ta be an effective taal sa these tests are nat used generally. The determinatian af antibadies to





the group A streptococcus in the blood is on excellent ond relioble way to moke o diognosis, but is not used frequently becouse the test requires o comporison between blood drawn ot the time of illness ond blood drawn 2 to 3 weeks loter, which precludes its use to diagnose ocute diseose. The only relioble way to diognose on ocute strep infection is to demonstrate the streptococcus in the throot. The time-honored woy to do this is by o throat culture. Since the throot culture requires 18 to 24 hours before results ore known ond is relotively expensive, efforts have been made to find other woys to demonstrate the streptococcus in throots. None of these has been developed to the point thot it is satisfoctory for clinicol use, so the throot culture remoins the method of choice.

The time-honored way to demonstrate strep in the throat is by a throat culture.

A properly obtoined ond properly processed throat culture will reveol streptococci in about 90% of strep throot coses. People with untreoted strep throats will continue to "corry" the streptococcus in their throots for several weeks or even months ofter the ocute illness. Fortunotely, ofter o short time the streptococci thot ore corried in this woy do not seem to horm the carrier ond do not spreod readily to others. On occosion, though, this corrier stote poses o problem to the physicion in interpreting throat culture results. In these coses the doctor must assess the clinicol and epidemiological findings ond moke o decision regarding the significonce of the positive throot culture.

Making the Diagnosis

The physicion mokes the finol diagnosis of o strep throot using oll ovailoble tools — epidemiologicol doto, clinicol findings and the throot culture. Becouse of the cost of o throot culture, much effort hos been expended in developing methods thot help physicions decide which potients with sore throots ore likely to have o strep throot ond thus should hove their throots cultured. These monogement plons or protocols (colled clinicol olgorithms) ore bosed on studies showing the percent of patients with certoin epidemiological ond clinicol findings who hove a positive culture. For exomple, the child under 2 yeors of oge with fever ond o runny nose olmost certoinly doesn't have o strep infection ond need not be cultured. Also, the odult with o cold ond cough is unlikely to have o strep throot and should not hove o culture.

Physicions are encouroged to use ovoiloble clinical ond epidemiological methods in on orgonized woy in the monogement of potients with sore throots. A few potients, such os those with o history of previous rheumotic fever, those with scarlet fever or those who ore more severely ill, con be treoted immediotely. In such coses the throot culture con be used to confirm the diognosis. Potients who ore considered to be ot high risk for o strep infection becouse of the epidemiologicol ond clinicol findings should be cultured ond only those with positive cultures should be treoted. On occosion the physicion moy stort the potient on an orol ontibiotic while owoiting throot culture results. If the culture is negative, the ontibiotic should be discontinued.

In the post when rheumotic fever wos more of o problem, throot cultures were used extensively to identify people with positive cultures who would then be treoted. It is the feeling todoy thot these extreme efforts ore no longer necessory or even odvisoble. For instonce, it is no longer recommended thot fomily contacts of sore throot coses be cultured unless they ore symptomotic. Throot cultures following treotment to detect treotment foilures ore no longer recommended if the potient no longer hos symptoms.

Treatment

Specific. Penicillin remoins the drug of choice for treoting potients with strep throots unless they ore ollergic to it. A single injection of o long-acting penicillin (benzothine penicillin) is the preferred ond most

. . . rest, fluids, soft diet.



reliable treatment. Because this shat can be painful, many physicians prefer ta use aral penicillin instead. This is satisfactory therapy if the penicillin is taken as directed for a full ten-day period. The big prablem with oral medications is that patients tend to farget them after they feel better, which usually occurs with strep thraats after twa to three days.

For the patient wha is allergic ta penicillin, oral erythromycin is the antibiatic of chaice. For the rare patient wha cannat talerate either af these twa drugs an aral cephalasporin ar clindamycin can be used. Ten days of therapy are necessary for all af these oral medicatians. The sulfonamides and tetracycline drugs do nat eradicate strep fram the thraat and are not acceptable forms af therapy.

Non-specific. Patients with strep thraats alsa benefit from nan-specific treatment. Rest is essential and some patients may need ta stay in bed far several days. Sufficient fluids ta prevent dehydratian should be encouraged and the patient can have a saft diet as tolerated. Aspirin or acetaminaphen can be used ta relieve the pain of sore thraat or painful lymph nades. Gargles with a warm salt solutian may help relieve the painful throat. Because af the cammonness of strep thraats, nothing is gained from isalating the non-haspitalized patient with a strep throat. Children can return ta schaal and adults ta wark as soon as they feel well enaugh ta do sa.

The Cost of Sore Throats

Because upper respiratory infections are sa camman and the cast af medical care so great, much attention is being paid ta the mast ecanamical way to manage patients with sore thraats while maintaining gaad standards of medical care. Physicians are encauraged ta use clinical algarithms so that their care af these patients is standardized at all times. Algarithms are especially useful for nurse practitianers and ather allied health persannel wha are assuming primary medical care in same areas. Terms such as "cost-effectiveness analysis" and "cast-benefit analysis" are being used to describe efforts ta develop the best treatment at the least possible cast. Because aur knawledge abaut strep throats and rheumatic fever is in a state of great flux, there is na consensus abaut the anly way ta manage sore thraats. The rules outlined above appear to be the best that can be affered taday, but changes will almast certainly accur in the future.

What Does the Patient Do?

It is not easy far patients, or parents af patients, with sare throats ta knaw what to do when the situation is sa complex. Prabably the most impartant thing far the patient ta know is that rheumatic fever is no longer the prablem that it ance was in the United States. This is leading ta a change in the strategy far managing sore throats, with a relaxation af same af the former vigaraus efforts used ta diagnase and treat strep throats. The move ta reduce medical care casts has accentuated the impartance of these effarts. In this climate the patient must remain in close communicatian with primary care physicians, so that mutually satisfactary management af sore throats in 1984 can be attained.

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Vitamins

Jim Worden, Pharm.D.

American cansumers spend aver three billian dollars a year an vitamin and nutritional products. Daes this mean that diet supplementatian and better health ga hand in hand? No, nat necessarily; in most cases, the American diet does not need supplementatian. Mast health authorities agree that attentian to a balanced diet and adequate caloric intake eliminates the need for supplemental vitamins for mast peaple.

Anather segment af the American public seeks vitamin therapy far relief ar cure of such illnesses as cancer, heart disease, and arthritis. Again, very few of these people will derive much benefit from such therapy. Miscanceptians surrounding vitamin use are bath plentiful and varied. This article reviews the actions of the different vitamins, the disease states associated with their deficiencies, the recommended daily intake af these nutrients, and identifies thase individuals mare prane to require vitamin supplementation.

Vitamins are chemically unrelated organic substances that play an essential role in the chemical machinery of the body. They are materials so universally available in diets that humans no longer have (or need) the ability to synthesize them. By definition, vitamins must be chemicals supplied from external sources.

Most people eating a balanced diet do not need to take vitamin pills. Normal persons can develop vitamin deficiency by eating peculiar diets, but you have to work hard to become deficient. Vitamins play such a specific role in body function that a deficiency in a specific vitamin results in a specific disease with resultant disability or even death. For example, a deficiency in vitamin C can result in scurvy, a rare disease in the U.S., but one that cauld result in death if left untreated. Healthy peaple da not need ta have their diet supplemented by vitamins. Sick persans may ar may not need supplementation.

Generally speaking, vitamins can be grauped inta two distinct categories: (1) fat-soluble vitamins which include A, D, E and K and (2) watersaluble vitamins B, C, niacin, and folic acid. Other vitamins such as pantothenic acid, biatin, chaline, and the biaflavinoids will not be discussed as their nutritional significance is not as well understood.

Fat Soluble Vitamins

Vitamin A (retinol) is necessary to prevent night blindness and drying of the conjunctiva, the mucaus membrane that cavers the eye. Warldwide, vitamin A deficiency is a leading cause of blindness in childhood. Pregnant women must take in enough retinol to avoid fetal malformations. Since vitamin A is a fatsoluble vitamin, most fatty foods contain it; fish, organ meats, cream, butter, eggs and milk are all excellent sources. Retinol is also available in carrots, squash, and dark leafy vegetables.

In the U.S., vitamin A deficiency occurs more often from an inability to absorb fat properly than from a deficient diet. Certain diseases such as cystic fibrosis and cirrhosis, and certain drugs such as cholestyramine, can cause fat malabsorption and consequently vitamin A deficiency. The U.S. recommended daily allowance for vitamin A in adults is 5,000 I.U. and 8,000 I.U. in pregnant or breastfeeding women. High doses of retinol should only be taken under close medical supervision. Vitamin A is stared in the body and high dases can lead ta a taxic state with thrabbing headaches, nausea, vamiting, dizziness, insamnia, and night sweats.

A promising yet largely investigatianal use of vitamin A derivatives has been in the preventian af certain cancers and skin disarders. Dases af vitamin A required ta attain these benefits, hawever, are alsa high enaugh to cause toxicity.

Vitamin D is necessary ta stimulate the absarptian of calcium fram the small intestine and, in canjunctian with ather body harmones, ta regulate the cancentration of calcium in the serum. Vitamin D can be synthesized if the skin is irradiated with sunlight. If sun exposure is insufficient, thaugh, vitamin D must be obtained fram the diet.

Deficiency af vitamin D in children can lead ta rickets, a disease characterized by soft banes and deformed jaints due ta a lack af adequate calcium in the bane. The adult disease equivalent to rickets is osteomalacia, an equally debilitating disease seen in patients with kidney disease, malabsorption syndromes or other endocrine problems.

Milk and milk products are the major sources of vitamin D in the U.S. diet. Other rich sources include eggs and fish. Most people obtain the recommended daily allowance of vitamin D in their diet and from exposure to sunlight. Adults should limit their intake to 400 I.U. per day. Doses greater than 1,800 I.U. may inhibit growth in infants. Symptoms of an overabundance of vitamin D include anorexia, weakness, nausea, vague aches, weight loss, hypertension, anemia, and possible irreversible kidney failure. Patients who feel they need additional vitamin D should seek the advice of their physician or pharmacist.

From the Deportment of Pharmacy Services, Pitt County Memorial Hospitol, Inc., Greenville 27834.

Vitamin E. Althaugh the biachemical function af vitamin E is still unclear, it is thaught ta pratect vital membranes fram axidative damage. There appears ta be na well defined vitamin E deficiency state in adults and, since infant farmulas are supplemented with vitamin E, an infant deficiency canditian is alsa rare. Faads rich in vitamin E include green vegetables, whale grains and margarines.

The U.S. recammended daily allawance for vitamin E is 30 I.U. far adults, 10 I.U. for children and 5 I.U. far infants. An average American diet pravides 15-20 I.U. af vitamin E. Of the fat-saluble vitamins, vitamin E appears ta be ane of the least toxic in large amounts, although it is impartant ta watch for interactians with anticaagulants and iron products. Claims far megadose vitamin E therapy impraving circulatary disarders, heart diseases, and athletic and sexual perfarmance are largely unfaunded.

Vitamin K. Green leafy vegetables, dairy praducts, and fruits constitute the majar dietary saurces af the fat-saluble vitamin K. But mast vitamin K is produced by micraarganisms in the intestine. Bleeding is the mast camman symptom af vitamin K deficiency and it is usually assaciated with a seriaus illness. Occasionally, a vitamin K deficiency is seen in a person wha takes antibiatics that may inhibit the organisms responsible for vitamin K synthesis. Hawever, this is only seen if dietary intake is insufficient. Other passible inhibitors of vitamin K absorption include liver disease, malabsorptive syndrames, and drugs such as chalestyramine resin, mineral oil and aral anticaagulants.

Very few af the over-the-caunter vitamin preparations contain vitamin K. There is na recammended daily allawance far the vitamin, but a daily intake af 70-140 mcg is cansidered safe and effective. Narmal U.S. diets cantain 300-500 mcg of vitamin K per day.

Water-Soluble Vitamins

Vitamin C (ascorbic acid). As mentianed earlier, vitamin C is necessary ta prevent scurvy. Scurvy causes impairment af waund healing and is manifested early an by anarexia, weakness and jaint and muscle aches. Bleeding inta the skin, muscles, jaints, gastraintestinal mucasa, and majar argans can also accur. Death may accur if the disease is left untreated. In infants, ascarbic acid deficiency may cause retarded grawth and development, as well as anemia and hemorrhaging.

Fresh fruits and vegetables are goad saurces of vitamin C, and a normal diet cantains several times mare than the 10 mg/day vitamin C needed ta prevent scurvy. The U.S. recammended daily allawance for ascorbic acid is 60 mg for adults, 40 mg far children and 35 mg far infants.

Vitamin C has been used far other medicinal purpases. Although reparts that vitamin C prevents calds have been made far same time, wellcantralled studies have failed ta shaw a significant benefit. Given in large dases (1-10 gm), ascarbic acid is generally safe; hawever, significant interactians may accur with drugs ar lab tests. Urine glucase tests may give false readings if given while the patient is taking megadose vitamin C. In additian, the actians and/ar toxicities of several antibiotics, including the sulfa drugs, may be affected by ascarbic acid. Yau shauld cansult your pharmacist ar physician ta determine whether ingestion af large amounts of vitamin C will have an effect on medicatians or tests yau may be using.

Vitamin B-1 or thiamine is required far bath carbahydrate metabolism and nervaus system functioning. Beriberi, the thiamine-deficiency state, is rare in the U.S. but accurs in areas where palished rice is the majar ingredient af the diet. Heart failure, swelling, weakness, and numbness in the fingers and taes canstitute passible symptams af this disease. Infantile beriberi may alsa accur, mimicking the picture af meningitis. A mare camman presentatian is in an alcahalic whase diet is unbalanced. A severe metabalic canditian (Wernicke-Karsakaff syndrame) may be seen in this type af persan. Psychasis, permanent neuralagic damage and even death can result if this syndrame is left untreated.

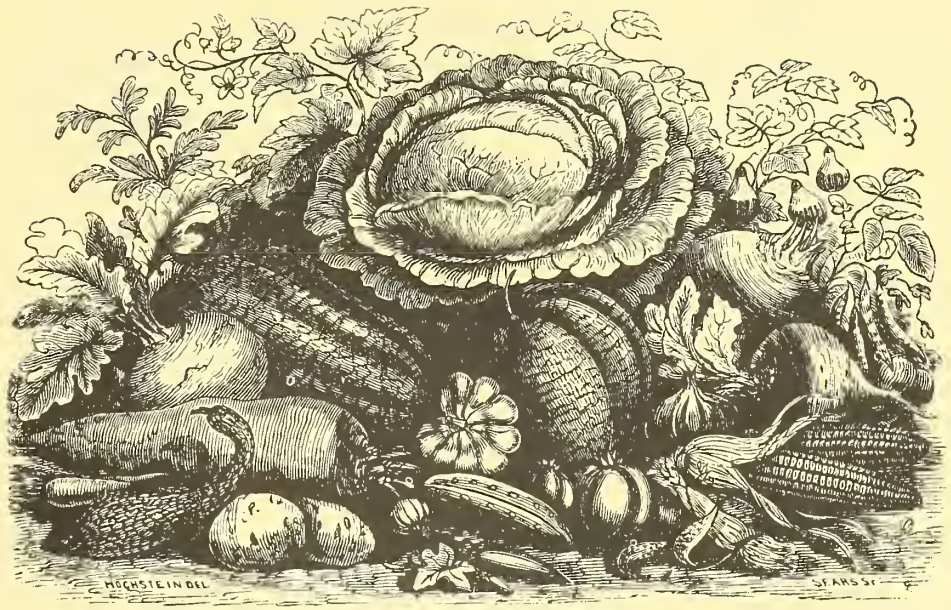
The recammended daily allowance af thiamine is 1.5 mg far children aver 4 and adults, 0.7 mg for children under 4, and 1.7 mg for women during pregnancy and lactatian. Excessive thiamine is rapidly eliminated in the urine and is relatively safe, as are many of the water-saluble vitamins.

Riboflavin (vitamin B-2) is invalved in numeraus reactians necessary far cellular grawth and metabalism. Symptoms af this deficiency include inflammatian af the skin over joint areas, scaling af the lips and mauth and inflammatian af the tangue. This may pragress to a generalized dermatitis aver the rest af the bady.

Sources rich in vitamin B-2 include eggs, fish, meat, liver, whole grains and milk. The U.S. recammended daily allawance far this vitamin is 1.7 mg far adults and 2 mg far pregnant or lactating women. Excess ribaflavin is excreted in the urine.

Niacin and niacinamide are vitamins that are necessary components of the cellular respiratary system. Humans synthesize about half their niacin from the amina acid tryptaphan. The ather half must be supplied fram their diets. The once common disease, pellagra, which is the niacin deficiency state, is now rare in this country. It is still seen in alcahalics, the elderly, and those on unusual diets. This disease is characterized by the "3 Ds": diarrhea, dementia and dermatitis.

Lean meats, liver, fish, whale grains, green vegetables, and legumes are foads high in niacin content. The recammended daily allow-



ance of niacin is 20 mg. High doses can cause serious side effects. Gastrointestinal irritation, cardiac arrhythmias, impaired liver function and facial flushing can be associated with high doses of niacin. Niacinamide does not produce the flushing that comes from the use of niacin. High dose niacin is used to lower the concentration of cholesterol and triglyceride in the plasma.

Vitamin B-6 or pyridoxine is necessary for the metabolism of amino acids or protein in the body. In infants pyridoxine deficiency is manifested by convulsive disorders and irritability. Adults show the same signs and symptoms as they would with niacin and riboflavin deficiencies (dermatitis, neurological defects).

Foods with a rich supply of pyridoxine include meats, nuts, bananas, potatoes and cereals. Most U.S. diets provide the recommended daily allowance for vitamin B-6, which is 2 mg for those over 4 years of age, 2.5 mg for pregnant or lactating women, and 0.7 mg for children under 4 years old. Pyridoxine is generally considered nontoxic.

There are several noteworthy drug interactions possible with pyridoxine. The anti-tuberculosis drugs isoniazid and cycloserine, as well as the blood pressure medication hydralazine, can antagonize pyridoxine to some degree. On the other hand, pyridoxine may reduce the therapeutic effect of levodopa, a drug for people with Parkinson's disease, if both are taken. If you are taking any of these drugs, consult your pharmacist or physician to determine if they might interact with pyridoxine.

Cyanocobalamin or vitamin B-12 is required for the metabolism of fats, for cell division, and for recycling other necessary vitamins such as folic acid. A deficiency in this vitamin can result from a defect in absorption or from inadequate intake of the vitamin. A deficiency of B-12 causes the clinical picture we call pernicious anemia. Because the body conserves and stores this vitamin, the deficiency state may require many years to develop.

Animal protein is the largest contributor of vitamin B-12 content in the diet. Small amounts may also be found in legumes such as peas and beans. Because of the lack of B-12 in vegetables, vegetarians who consume no meat at all are at a risk of developing a deficiency state and should consider supplementing their diets with vitamin B-12. The U.S. recommended daily allowance is 2 mcg for infants, 3 mcg for children, 6 mcg for adults, and 8 mcg for pregnant or lactating women. Vitamin B-12 has little therapeutic benefit except in people deficient in the vitamin. Even in large doses this vitamin possesses little toxicity.

Folic Acid. In the body folic acid serves approximately the same function as vitamin B-12. In particular, folate is important in the biosynthesis of required components of cells. Vitamin B-12 is necessary for the regeneration of folic acid in the body. Therefore vitamin B-12 deficiency can result in folate deficiency which presents the same way as vitamin B-12 deficiency with mouth irritation, diarrhea, nervous system manifestations, and anemia. Causes of this deficiency are also similar to those of B-12 deficiency (poor diet, alcoholism).

Foods with high folic acid content include fresh vegetables, liver and organ meats. As with other vitamins, cooking, canning or long exposure to heat may destroy much of the vita-

min content. The U.S. recommended daily allowance for folic acid is 0.1 mg for infants, 0.2 mg for children, 0.4 mg for adults and 0.8 mg for pregnant and lactating women. Toxicity with folic acid is almost nonexistent.

As with several other vitamins, there can be significant interactions between folate and certain drugs. Methotrexate (a cancer drug), phenytoin (an anticonvulsant), oral contraceptives and trimethoprim (an antibiotic) may all cause antagonism of folic acid in the body. In addition, folic acid may reduce phenytoin concentrations. Consult your health professional if you have questions about any drug interactions with folic acid.

In summary, most vitamins fulfill a very specific role in the maintenance of normal body function. The amount of vitamins needed is small and an increase in the vitamin intake beyond what is required to carry out the specific function results in no benefit. Moreover, their deficiency causes very specific symptoms in areas of the body most dependent upon that vitamin and it is easy to determine that the person is not healthy. Fortunately, these deficiency states are not seen frequently in the United States, most likely because Americans have a dietary intake adequate in vitamin composition. There are certain segments of the population, however, who are known to be at risk for vitamin deficiencies unless vitamin supplementation is added to their diet. These include the following categories:

1. Increased metabolic requirement: pregnancy, lactation, infants, severe injury, major surgery, and severe infection.
2. Poor absorption: prolonged diarrhea, severe gastrointestinal disorders, malignancies, cystic fibrosis, etc.
3. Inadequate dietary intake: the aged, alcoholics, and the impoverished.
4. Other: patients on certain drug therapy such as oral contraceptives, selective antibiotics, etc.

Selection of a multivitamin for people who fall into the above groups should be based on attempting to supply approximately 100% of the recommended daily allowance for each vitamin needed. Remember, excessive doses or higher potency brands will not offer any additional benefit, can cause toxicity (especially the fat-soluble vitamins) and usually will be more expensive than conventional supplemental vitamins. Vitamin supplementation is not a substitute for a well-balanced diet.

Editor's Note: My wife and I have enjoyed and are enjoying life. Savings from not purchasing vitamins or cigarettes contribute to our happiness.

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Investment Advice to the Fairest of the Fair
The Perspective of an Ophthalmologist

Banks Anderson, M.D.

Frankly this is a racist prospectus. It is targeted at Caucasians of north European stock but others may read it and chuckle at paleface absurdities. It begins with a fairy tale:

Once upon a time, there lived the most beautiful of women, the fairest of them all. Her lips were red as the ruby, her hair black as the raven, her skin as white as the new fallen snow, her name Snow White.[1] For centuries swains were enraptured by such snowy whiteness tinted only with the rosy blush of modesty. Needless to say every belle did her best to preserve this purity of complexion. Wide brimmed hats, long sleeved blouses, shoe top dresses, even gloves were summertime garb. Many even carried head shading parasols . . . those that could.

Many could not. Before 1850 the economy was agricultural. The poor worked the fields sun-up to sundown, especially when the sun was high in the growing season sky. An athletic tan could only be avoided by wealthy ladies who had no need to brave the mid-day sun with mad dogs, the poor, and a bumpkin English squire or two. The ambiance of affluence dictated the allure of the pallid epidermis. Too often the poor were semi-starved and gaunt while the aristocracy ate well; pleasing plumpness and rotundity were also hallmarks of the leisured classes. Rubens painted the sexiest of women, well upholstered roundness in snow white skin, and the males of the day hung these ideals in their billiard rooms and salons. Nail-ups as it were.

From Duke University Eye Center, Durham 27710.

What so changed the ideal woman? Why is now the thin, tanned, athletic body with sun-bleached hair in such vogue? You have, no doubt, guessed. The allure of affluence again. In the twentieth century where does the wage serf work? Indoors. Where do the affluent go in the winter? Palm Beach, Cancun, Aspen, St. Moritz. Now the stigma of wealth is the brown body while the working class has moved out of the fields and into factories and offices. Their former nut-brown countenances now become snow white and their derrieres rotund from tending their indoor stations. The poor pallid things seek out water reflections, arrange aluminum panels, shed every scrap of clothing the law permits, abandon the hat (even in the cathedral) and otherwise do their best to attain the tanned allure of affluence. But what a price!

Malignant melanoma of the female leg, almost unknown before, now appears.[2] Carcinomas of the face and arms become the commonest cancer.[3] Dermatologists and plastic surgeons busily freeze, tuck, and lift attempting to repair their sun-ravaged visages. Worn old before their time, the wrinkled splotched faces of these Sun Browns thicken and sag from actinic elastic tissue damage and grow excrescence after excrescence attempting to repair the irreparable. Snow White knew that apple or no, her prince would come and kiss her smooth pure-white face. Today's older Sun Brown may find that today's prince passes by her mottled wattled cheek and seeks a younger smoother one instead.

If beauty is only skin deep, and is valued, why then should we parents tolerate our twelve year olds frying their skins, basking like lizards at the pool or beach? There is nothing inborn or even rational about the fickle Caucasian male's current preference. When computers run our factories and the masses are turned out again to the streets and fields while managers and directors operate their indoor data terminals, Snow White may once again become the epitome of skin deep beauty. Girls, this may come sooner than you think, so save your skins! Protect your investment!

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SWEAT OR NO SWEAT

Peter W. Heald, M.D., Claude S. Burton, M.D., and J. Lamar Callaway, M.D.

"Harses sweat, men perspire." This well-known adage demanstrates aur peculiar relatianship with sweating. Sweat is essential ta aur everyday life. Yet we try ta refine it with fashianable terms, cover it with fragrances, desiccate it with powders, cushian it with Odar Eaters, feminize it with Secret, masculinize it with Right Guard, only ta wark up a sweat during our haurs af relaxotian.

Our skin produces two types af sweat. One af these is called eccrine sweat which is produced aver the entire bady surface. This is distinct from the secand type, knawn os opocrine sweat, which is praduced in the underarm area, the grain, and rarely elsewhere. The sweat glonds that praduce these two types af sweat differ in their structure, function, and final product. Eccrine sweat is clear fluid readily produced in respanse to heat ar ematianal stimuli. These glands continually produce sweat and can achieve praductian rates on the order af quarts in athletes during o warkaut. Apocrine sweat, hawever, is a cloudy, thicker material that is more adherent to the skin. Apocrine sweat cantains mare materials such as iran, fats, and a fatty substance knawn as lipafuscin. Many bacteria thrive an the material in apacrine sweat. Alsa the apacrine glands cannat cantinually praduce sweat. After a glond is emptied it sametimes takes up ta a day ta relaad with apacrine sweat.

Eccrine sweat functians primarily ta caal the bady and maintain a minimal amaunt af hydration for the skin. These are benefits that ga largely unnoticed during the course af a day. Hawever, when these sweat glands are averpraducing they are quickly naticed.

Excessive sweating, knawn as hyperhidrasis, can be disabling althaugh it is rarely due to a specific disease. Hyperhidrasis is defined by our perceptian of how much sweat is needed. Perhaps the bady senses the need ta sweat before we can consciausly appreciate this. In many cases, such as in the caurse af a fever, it is appropriate to have hyperhidrasis. Nonetheless at times the bady reacts as if there is reasan to sweat, eccrine sweating is triggered and aur variaus anti-perspirant routines begin.

If the sweating is not symptamatic enough a patient may present with o problem that is actually a camplicatian af excessive eccrine sweating. Fungus and yeast infections af the skin accur in excessively maist areas such as the feet ar in the groin. Failure to control excessive moisture will lead to mare frequent recurrences and slawer clearing af these infections. Excessive sweoting over the trunk may lead ta the production af miliaria (prickly heat). This was frequently found in aur traaps in Vietnam. Nat only is this produced by excessive sweating but it is also contributed to by external pressure an the sweat glands. In Vietnam this may have been due to carrying backpacks and ather equipment. In the haspital miliaria is frequently seen an the patient's back, especially during pralanged bedrest and fever.

Another, althaugh infrequent, complicatian af sweoting is contact dermatitis. Many peaple wauld nat realize thot they are allergic to an elastic in their underwear or a clothing dye in their underclothes were it nat far the eccrine sweat which washes into this material and washes the allergic material out and onto the skin where the dermatitis then accurs. Again, contralling sweating in this setting helps in managing the patient. While eccrine sweoting has little ta da with eczema af the honds and feet, the latter disarder still gaes by the name dyshidrosis (abnarmal sweating). Indeed, patients with this candition often have excessive eccrine sweating alang with their hand ar foat eczemo. This overreoctivity af the sweating system is analagaus to the aver-reactivity of their skin which can be irritated by all but the mildest af soaps and lations.

The appraach to treating hyperhidrosis is ane af trial and error. Several agents are very gaod ot absarbing the extra sweat, and far many patients this will suffice: a drying pawder such as Zeasarb is very good when applied to the areos being drenched an a regular basis; far the feet, pads such as Odor Eaters ore also absarbent.

One hame remedy that has been successful for peaple wha excessively praduce sweat is ta use tepid tea in a bawl ta saak the hands, feet, ar whatever port is bathered by the hyperhidrasis. Da this far approximately twenty to thirty minutes twice o day. There is an agent in the tea which clags sweat glands.

Twa agents that hove been used ta clag up sweat glands are the aldehydes (glutaraldehyde and formaldehyde) and aluminum chlaride. These agents must be prescribed and applied under the guidance af o physician because many reactions can accur in the inexperienced user. Bath af these praducts caagulate pra-

Fram the Department af Medicine, Duke University Medical Center, Durham 27710.

tein in the sweat ducts leading to a blockage of the duct and a consequent decrease of sweating. The glutaraldehyde has a side effect of making the skin it is applied to turn dark.

While most patients may actually believe that there is a pill that could be taken for sweating, this is not the case. Probanthine is a medication that has had a very unpredictable response. Some patients may take this medicine and hardly sweat again whereas others seem to be untouched by it. In those who do have an effect there are also the side effects of dry mouth and flushed face.

The latest form of therapy for sweating is the iontophoresis machine. This is a machine that passes a direct current through the skin and in that process somehow damages the sweat ducts. These machines run from $100 to $300 and may be purchased by the physician or patient. Treatments typically are conducted three times a week, and after two or three weeks the patient can be relatively sweat-free in the area treated with the iontophoresis machine for up to two months. The current generator is plugged into the wall outlet and a pan of tap water is hooked up to the machine. The patient then places the part of the body to be treated into the pan and the machine is turned on. For tough to treat areas there have been adaptations made such as wiring a brass door knob which can then be placed into the area (the underarm, for example) for delivery of current. It is not clear why this type of treatment works since the sweat glands appear unchanged. However, it has been well-documented that this does decrease sweating.

The most popular type of sweating is that of apocrine sweating. The reason apocrine sweating is the subject of so many television advertisements is its ability to produce a foul odor. Apocrine sweat itself does not smell but bacteria grow readily in the rich materials found in the sweat. The bacterial products are responsible for the odor and all of the embarrassment that this brings. In people with excessive eccrine sweating there is usually a minimal problem with apocrine sweat odor. This is because the eccrine sweat effectively cleanses the underarm by drenching it with the clear fluid which washes away the bacterial products.

Because the bacteria are necessary for apocrine sweat odor, antibiotic agents have a role in the management of problems related to apocrine sweating. Topically applied Clindamycin, Tetracycline, and Erythromycin have all been noted to decrease bacterial counts and improve underarm odor in the general population. The most common commercial agent used for underarm perspiration is aluminum chloride, which leads to blockage of the sweat glands and decreased sweating. Excessive underarm sweating is most likely due to eccrine sweat, and other agents used in eccrine sweating disorders may also be useful: the drying powder, glutaraldehyde, and iontophoresis.



IT'S GETTING TOUGHER FOR NANCY RAY TO BE A MOTHER.

Nancy Ray has multiple sclerosis.

Every day it becomes harder for her to see. Harder for her to walk. Harder to do the things she wants to do for her family.

Four years ago, Nancy Ray was young and healthy. She was a mother with a four-year-old son, a teacher, a writer for educational TV.

Then, like about 200 young adults every week, she learned she had MS.

Multiple sclerosis destroys the myelin covering that surrounds nerve fibers in the brain and spinal cord. Messages to and from the brain get lost as they travel through the damaged areas. So your eyes, arms, legs don't do what you want them to do.

MS can be mild. Or it can be severe. Once you've got it, you've got it for life. Most days, Nancy Ray can get around with a walker. With a lot of time and effort, she can even prepare meals for her family. Some people with MS aren't that fortunate.

The National Multiple Sclerosis Society is helping people with MS live with MS. And funding research for a cure, all over the world. We can do it, but only with your help.

Please give generously. It's tough enough to be a mother without MS.

NATIONAL MULTIPLE SCLEROSIS SOCIETY

205 East 42nd Street
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JUST WHEN YOU'RE STARTING TO LIVE, MS CAN STRIKE.

Mimi, Violetta and The "Captain of All The Men of Death" INH (Isoniazid) Poisoning

Ronald B. Mack, M.D.

CERTAINLY one of the major medical advances in the last half of the 20th Century has been the discovery of medications to combat one of the scourges of mankind — tuberculosis. This disease has been euphemistically referred to by many names throughout history, e.g., the "white plague," "consumption," etc., but my favorite is the name given to tuberculosis by John Bunyan. Mr. Bunyan, many of you will recall from English Lit 101, was the 17th Century British author who wrote *The Pilgrims Progress*. This famous writer referred to "consumption" as "the caption of all the men of death" and this beautiful description is still being used in our century. It was not until 1882 that Robert Koch isolated the tubercle bacillus. Thus before that time writers had to invent names to refer to this disease in very descriptive terms to imply its deadliness.

The great doctor-essayist Lewis Thomas in his recent book, *The Youngest Science: Notes of a Medicine Watcher,*[1] describes his own medical school training in this country between the two world wars and reminds us that the "two great hazards to life" in those days were tuberculosis and tertiary syphilis. He further relates that "these were feared by everyone, in the same way that cancer is feared today." Probably some of you remember the manner in which tuberculosis was treated before World War II — the sanitaria, the mountain resorts, fresh air, sunshine, nutritious diets — hoping and waiting for the body to heal itself. If these methods failed one often resorted to iatrogenic lung collapse (obviously only for pulmonary TB) utilizing induction of pneumothorax, or rib removal over the affected area, or my absolute favorite — plombage — the implantation of methylmethacrylate balls (like ping-pong balls). We've come a long way, baby!!

Since the early 1950s we have been able to use isoniazid (INH) in the battle against the "captain of all the men of death." INH remains the cornerstone of the treatment for active tuberculosis as well as the drug of choice for prophylaxis therapy of positive TB skin test reactors. INH, as helpful a drug as you can imagine, is a bad dude if taken in overdose. The morbidity and mortality following major INH overdose are very significant indeed. (By the way, lest we forget, tuberculosis is not a disease only of the past; this disease and malaria are the most widespread and persistent human infections in the world at large even as we speak.)

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

When INH is ingested therapeutically it is rapidly absorbed, primarily in the small intestine, and produces peak plasma concentrations in 1 to 2 hours. It is important for our purposes to recall that INH significantly penetrates the CNS. The most important pathway quantitatively for INH metabolism involves *acetylation*. (Is this biochemistry really necessary?) Just as you can divide all children into two groups — those that like peanut butter and those that don't — you can divide INH acetylators in two groups — *slow* and *fast*. Your individual acetylator status is genetic. *Slow acetylators* are homozygous for the regressive gene and have an INH half-life therapeutically of 2-4 hours whereas *rapid acetylators* are either heterozygous or homozygous for the dominant gene. The INH half-life for rapid acetylators is 0.7-2 hours. About 60% of all Caucasians and blacks are slow acetylators whereas about 90% of orientals and Eskimos are rapid acetylators. It is probably better to be a rapid acetylator if you accidently overdose on INH. Isoniazid has a volume of distribution (V_D) of 0.6 1/kg and has negligible protein binding.

INH is dispensed in tablets of 50, 100 and 300 mg. As little as 1.5 grams taken acutely can cause toxicity in an adult (Gosh, that's only five 300 mg tablets!!). Acute ingestion of 6-10 grams by an adult (20-30 of the 300 mg tablets) can cause severe toxicity and even death. Ingestion of 15 grams or more acutely by an adult is often quite fatal if untreated.

The clinical triad of isoniazid overdose consists of *repetitive seizures, metabolic acidosis* and *coma*. The clinical features of an acute INH overdose begin as early as 30 minutes after ingestion or as late as 120 minutes (for a few, up to 4 hours post ingestion). *The initial signs and symptoms* are quite non-specific, namely: nausea and vomiting, dizziness and blurred vision, ataxia and increased deep tendon reflexes. Rather quickly the patient can lapse into coma and experience repetitive seizures (generalized or focal) and then again quite rapidly progress to intractable coma and death by respiratory or cardiac failure. Hyperpyrexia is a common feature. Severe hypotension, oliguria or anuria can also occur.

Without question, the *convulsions* and the *metabolic (lactic) acidosis* are the most dramatic systemic effects of INH overdose. The seizures are frightening and typically quite repetitive. The alleged cause of the seizures is a fascinating story, at least to me. (But then I am fascinated

by the chromosome status of Grammy Award Winners.) One of the neurotransmitter systems that holds us together involves the proper functioning of the glutamic acid-gamma-aminobutyric acid system otherwise known as GABA. GABA is necessary for proper synaptic transmission in the CNS. Vitamin B_6 (pyridoxine) is vital to the production of GABA. If your B_6 is decreased then your GABA is decreased. INH decreases brain GABA levels by inhibiting the activity of pyridoxal-5-phosphate (necessary to metabolize GABA), and also by depleting the body's store of B_6. As little as 15 mg/kg of INH can lower the seizure threshold and 35-40 mg/kg produces spontaneous seizures in man.

The *metabolic acidosis* that occurs in INH toxicity is unique in that it is a *lactic acidosis*. Metabolic acidosis usually results from an accumulation of acid (other than carbonic) in the extracellular fluid or from a loss of bicarbonate in the extracellular fluid. Metabolic acidosis can be divided into two great groups; those with and without an *anion gap* (Is this really necessary? You can skip this part if you want to and resume reading in the section on treatment). Simply stated, the anion gap is calculated by adding together the extracellular concentrations of sodium and potassium and subtracting the chloride and bicarbonate concentrations. The normal range is 8-16 mEq/l with a mean of 12 mEq/l [$(Na + K) - (Cl + HCO_3) = 12 \pm 2$ mEq/l)]. If the patient has a metabolic acidosis with an increased anion gap (> 12 mEq/l) then you can assume that there has been an accumulation of an acid other than carbonic, such as in salicylate intoxication, methanol or ethylene glycol poisoning, uremic acidosis, diabetic ketoacidosis and *lactic acidosis*. In lactic acidosis the serum lactate level exceeds the normal of 9-16 mEq/l. If your patient has a lactic acidosis and you suspect a poison remember that the drugs in overdose that will cause this problem are such drugs as INH, ethanol and phenformin, etc. INH probably blocks the conversion of lactate to pyruvate but probably a major cause of lactic acidosis in INH toxicity occurs secondary to the repetitive seizures. (This is an issue still being debated, i.e., what is the major cause of the lactic acidosis in INH overdose?). As long as INH levels are not readily available you can determine if a patient with an alleged overdose has a metabolic acidosis. If the patient also has an increased anion gap you should obtain a serum lactate. If the serum lactate is elevated and you have a patient with a lactic acidosis, then that narrows the overdose possibilities to such toxins as phenformin (an oral hypoglycemic agent which is no longer commercially available in the U.S.), carbon monoxide, cyanide, ethanol, methanol and INH (there are others that will produce this state as well). Knowing the patient has a lactic acidosis and obtaining a good history of what drugs the patient had access to should make the diagnosis in many cases.

The laboratory investigation of this overdose at minimum consists of arterial blood gas determination, serum lactate levels, electrolytes (mild hypokalemia is not uncommon), blood glucose (hyperglycemia can occur), CBC (leukocytosis is a frequent visitor), urine analysis (glycosuria and ketonuria may be present suggesting diabetic ketoacidosis). Most hospital labs do not perform serum INH levels but for rapid qualitative detection of INH and its metabolites the urine may be tested with a commercially available reagent-impregnated paper strip. If your hospital has the facilities the urine can be tested for the presence of an increased urinary excretion of pyridoxine. Some patients with INH overdose have a transient increase in the SGOT but this is not a constant finding. An EEG might be helpful. It is a good idea to measure the BUN and serum creatinine as renal function might be compromised.

By digesting all of the data thus far presented the treatment should be quite predictable although there are arguments, of course, concerning the best way to treat such a patient. Everyone would agree that the first step should be to make sure that you attempt to stabilize abnormal vital signs. I am sure that you are going to want to stop the seizures. The drug of choice is, you guessed it, *pyridoxine hydrochloride*. The purpose of giving pyridoxine is of course to increase the formation of the active coenzyme pyridoxal phosphate which is specifically inhibited by INH. The optimal dose of this antagonist should be at least equal to the maximum amount of INH allegedly ingested. The pyridoxine hydrochloride is mixed as a 5 or 10% solution with water and administered IV. If the patient allegedly swallowed 1 gram of INH you would give 1 gram of pyridoxine. Give the pyridoxine over a 5 minute period. You can repeat this dose at 5-20 minute intervals, if needed, in a comatose or convulsing patient. If you don't know the ingested dose start with 5 grams of pyridoxine. Many authorities believe that correcting the seizures corrects the lactic acidosis and they do not give sodium bicarbonate; others believe you need to correct the acidosis with sodium bicarbonate. Another variation of therapy concerns the use of diazepam. Some clinicians use this drug initially in an effort to stop the seizures; others would only use the drug if pyridoxine failed. Apparently diazepam increases GABA in the brain and also acts synergistically with pyridoxine. Once the life-threatening events are under control cautious gastric emptying should be performed as should the administration of activated charcoal and a saline cathartic. If all else fails, remember that INH has a small volume of distribution (< 1 l/kg) and very little protein binding and thus is a very good candidate for dialysis. Fortunately a patient with isoniazid overdose usually does not require this extracorporeal modality, i.e., the drug has a short life and pyridoxine is an efficient antidote.

I don't know about your classical tastes, but my two favorite operas are Puccini's *La Boheme* and Verdi's *La Traviata*. In both of these wonderful works, written in the 19th Century, the heroines die in the last act of what apparently is "consumption." In spite of their pulmonary compromise and obvious physical weakness, both Mimi (La Boheme) and Violetta (La Traviata) are able to bring tears to the eyes of the audience by singing beautiful arias at decibel levels that could shatter wine glasses. What would these composers do today? Would the female protagonists have to die from less dramatic late 20th Century diseases other than tuberculosis? Please spare me from operas where the heroine and main love interest dies from Legionnaires' disease, or perish forbid, AIDS!!

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EDITORIAL

Learning Without Words

Francis A. Neelon, M.D.

ONE year ago, when the first number of this *Journal* edited by Eugene A. Stead, Jr. appeared, he introduced a section that he called *"Learning Without Work."* Its purpose was to provide a means of communicating in brief, almost telegraphic form, those lessons that doctors learn every day from their patients. Practitioners are familiar with the phenomenon — they tell their colleagues about the exciting or novel or dramatic findings that come their way as they care for their patients. Dr. Stead hoped that those individuals who felt they had learned something new (or relearned something old) would be moved to communicate that lesson to the readers of the *Journal*. Indeed, I think it is clear from a year's experience that *"Learning Without Work"* has been a useful addition and has admirably succeeded in providing an otherwise unavailable vehicle for a kind of professional communication that "just comes naturally" to doctors.

Nevertheless, some actual or potential contributors seem uncertain about what topics are suitable or about what form their report should take. I believe that a touchstone is the following: Any time you say, aloud or to yourself, "What an interesting case" or "What a classic example of . . ." or "You should take a look at the patient in Room X" or "It's been a long time since I saw such a really nice demonstration of . . .," you have the germ of a contribution.

We are not looking for first (or second or seventy-ninth) cases of rare conditions or for exhaustive reviews of the literature with hundreds of references. Rather, we are seeking clear, concise descriptions of the learning that has come from experience. Case descriptions are helpful but they should not be presented in the stodgy or abstruse style favored by most medical journals, where the reader has to already be an expert in the field to comprehend what was done to the patient and why. We encourage authors to intersperse their case reports with editorial comments about how they approached the diagnostic and therapeutic process and about what they were thinking at critical junctures in the development of the case. This is the narrative style that doctors use when they talk to their colleagues in hospital corridors and we believe it is appropriate for *"Learning Without Work."* Case reports should be based on real events (that is, not "invented" for illustrative purposes), but irrelevant details ("The VDRL was negative," etc.) should be omitted. Normal ranges for diagnostic tests should be given in the text. Throughout, the author must make the case report convey to the reader those lessons that the patient taught the doctor and that generated the desire to write in the first place.

The case report will usually be followed by a succinct summary of what the author learned and a *few* salient references. Of course, some topics may not derive from case experiences. In such instances we will be happy to consider other forms of brief reports, usually arising from the author's experience with and thinking about some aspect of practical reality and taking the general form of "What I know now that I did not know before."

One final point. As the Chinese knew, but many of our contributors forget, one picture is worth $10^{\times}$ words! If you *see* something and want to write about it — take a photograph; draw a diagram; make a table! These visual aids convey information much more directly and concretely than any verbal message. They form a mental hook that grabs the reader's attention, and their impression is lasting. The reports by Li and by Pritchett elsewhere in this issue illustrate my point. Li's X-rays and Pritchett's diagram breathe life into their reports; without the visual impact, we'd be hard pressed to share the authors' sense of wonderment. Li and Pritchett have done us double service — by teaching us something we should know and by demonstrating the value of *"Learning Without Words."*

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EDITORIAL

Words of Wisdom from John Graham

John B. Graham, M.D.

I. Laws of Administration

The personal qualities of an administrator have an important effect on the outcome of events. The careful administrator leaves nothing to chance. He must be a successful "politician," in the non-invidious sense, always seeking common ground between contending parties and views. Many of his problems are ambiguous and he must make decisions that affect the lives and careers of others.[1] It is the rare person who can be a successful administrator for very long without alienating so many people that he becomes ineffective. If the admonitions below are carefully followed, the inevitable day of ineffectiveness will be postponed for many years.

1. Make decisions promptly but not precipitately after considering at least briefly the secondary and tertiary effects of each.

2. Reverse as few decisions as possible. Frequent reversals cause others to suspect that you are either (a) stupid, (b) indecisive, or (c) dishonest. The good administrator tries to be predictable and always keep his promises (and threats).

3. Cultivate "gravitas"[2] and "inscrutability."[3]

4. Be certain that paper work is accurate and delivered on time. Plan ahead to avoid the turbulence associated with unalterable deadlines. Try to conform to John Randolph's description of Martin Van Buren, the perfect administrator: "He rowed with muffled oars."

5. Treat your *subordinates* with scrupulous fairness and courtesy. Bend over backward to demonstrate your interest in their welfare. Defend them against outsiders, and never blame them for your errors. If you mistreat them, they will damage you later if only by sabotage.

6. Remember that your *peers and superiors* are highly intelligent, insecure, and slightly paranoid. Regard each one as a bomb on a hair-trigger which may explode at the most unintended slight. Peers and superiors are particularly concerned about their images and territories. Never threaten anyone's image or territory, except deliberately. Always make a careful analysis of benefits and costs before doing so.

7. Always be accessible and keep your appointments scrupulously. Not to be or do so suggests to others that you do not value them highly. (See paranoia above.)

8. *Always* have a witness present if you wish to be certain that a decision will withstand legal testing at a later time.

9. *Never* have a witness present if you may wish to issue a denial later.

10. Be careful about what you put in writing. Never say more than the absolute minimum.[4]

II. The Acquisition, Enhancement and Erosion of the Capital Asset, Good Will

Good will should be treated as a capital asset. It has peculiar properties, however. Acquisition occurs only once; enhancement is slow and difficult; and erosion may be very rapid. It differs from other capital assets in not being subject to the laws of interest; it does not compound while lying unused. In short, good will seems to be a unidirectional asset, only eroding with time.

When one joins an organization, he acquires a quantum of good will. (It is said of him that he is "in the honeymoon period" initially.) If carefully husbanded, his quantum may last for an entire career. Usually, however, it has been frittered away long before retirement. Rates of erosion vary from the almost zero rate of the careful, low-profiled person who never creates waves and does only favors for others, to the rapid rate characteristic of those who live from crisis-to-crisis at the expense of the nervous systems of their peers and subordinates.

Enhancement of good will is possible only for those who are in a position to do favors for others. The amount of enhancement is never great, however. The recipients of favors quickly forget that they have received favors and usually feel that there have not been any favors *lately*.

When representing clients, lawyers seem to be able to act as adversaries without breaking friendships. (Lawyers have been observed, however, to acquire permanent enemies when representing *themselves* in adversarial situations.) The young and naive have inferred from the courtroom experience of lawyers that they can practice adversarial tactics with impunity. Nothing could be further from the truth. The information networks of institutions are numerous and complex and institutional memory is cumulative. A price is paid in loss of good will with each adversarial encounter, whoever wins. Thus tactics of the type some-

[1] Devote your energies to selecting superior personnel. It is more rewarding and less traumatic than getting rid of inferior ones.

[2] Most people lack a sense of humor, especially when their own interests are concerned. If you conceal yours, they will find it easier to relate to you. Concealment also throws off persons having a sense of humor who will not know quite how to deal with you. There is a theory at the Harvard Business School that having hemorrhoids is advantageous for an administrator. The slightly pained expression that they give him makes interviewees think that he is listening attentively, and the pain provides him with insight into the problems of ordinary people.

[3] Locate a confidant for blowing off at intervals. Never explode publicly except deliberately, for its effect on others.

[4] This law does not apply to entrepreneurs. "Hype" is their natural mode of expression.

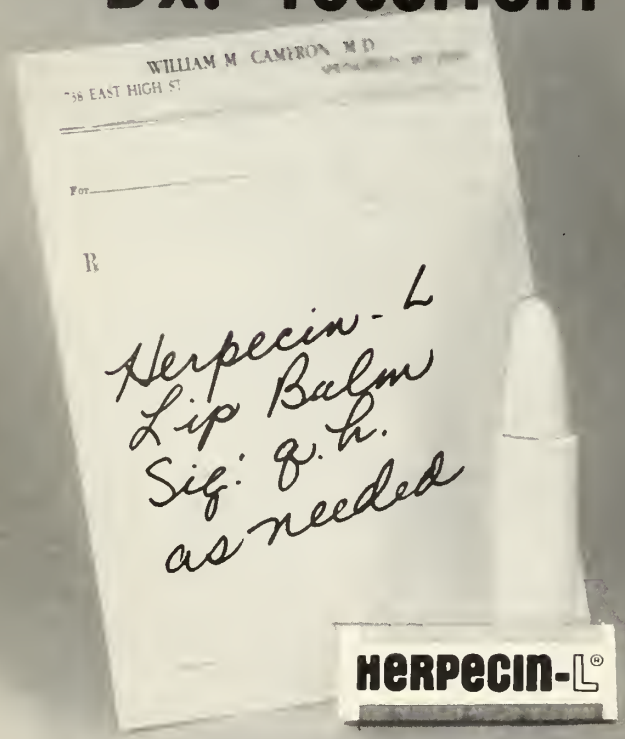
From the Department of Pathology, University of North Carolina, Chapel Hill 27514.

times referred to in the U.S. as the "northeastern style" can rapidly erode a stock of good will. The practitioner of adversarial tactics may suddenly discover that he lacks influential friends when he needs them most. This, of course, is the prudential basis for husbanding good will.

Good will may erode to zero, even become a negative quantity. When it becomes negative, it is referred to as "hostility." Once an individual becomes the general object of hostility, he becomes ineffective and must be either (1) put out to pasture, (2) discharged or (3) transferred. If such a person is to regain good will as a significant positive asset, he must change institutions, preferably moving to one sufficiently far removed that his reputation is not known. Such individuals are generally poor prospective employees, however, because their characters are usually fixed, and they will probably get into the same difficulties in a new institution.

There is an exception to all these rules. They do not apply to *STARS!* A STAR is universally respected, and respect may be a fully adequate substitute for good will. (A true STAR can get away with being an absolute bastard.) There is a tragic exception here, however. This is the case of the individual who thinks that he is a STAR but whose luminosity is less than he thinks. He may erode his good will asset under this mistaken impression and discover too late that it has been exhausted. Then he is in the predicament of a universally-recognized son-of-a-bitch.

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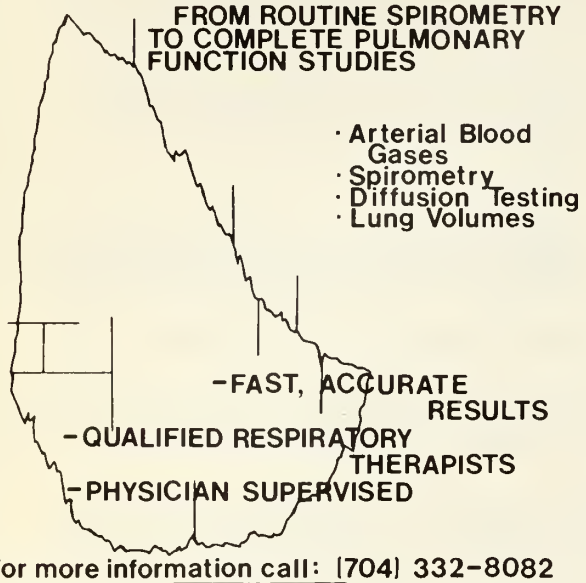
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BRIEF SUMMARY

PROCARDIA® (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: **Excessive Hypotension**: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: **General Hypotension**: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients; transient hypotension in about 5%; palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange/ soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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J-4044 January 1984

When Is a Stomach Bubble Not a Stomach Bubble? Answer: When It Is an Abscess!

James T. C. Li, M.D., Ph.D.

IN medicine, as in life, things are not always what they appear to be. In this report, an innocuous-appearing stomach bubble turned out to be part of a fatal illness. There were radiographic clues that might have tipped us off to the presence of a left subphrenic abscess.

This 66-year-old black man, who had lost 60 pounds in the last six months, had had cramping periumbilical pain for four weeks with mild post-prandial nausea and vomiting but no hematemesis. One day prior to admission, the patient developed fever, chills, and generalized weakness. He had a history of well controlled Type II diabetes mellitus and mild hypertension. There was no history of abdominal surgery.

The patient was in no acute distress. His temperature was 38.9 degrees Celsius, his pulse was 104/min and respirations 20/min. Pertinent findings on physical examination included bibasilar rales and a vague fullness to palpation in the left upper quadrant. There was occult blood in his stool.

The hematocrit reading was 30% and white blood cell count was 19,800 per mm^3 with a left shift. The chest X-ray (figure 1, left panel) revealed small bilateral pleural effusions and an elevated left hemidiaphragm. Initially, neither the Emergency Room physicians nor the radiology resident commented on the stomach bubble.

A few hours later, the radiology attending noted that the featureless borders of the air-fluid level extended more laterally than usual. A limited upper GI series using water soluble contrast (figure 1, right panel) showed a 10 cm air-fluid level in the left upper quadrant distinct from the normal stomach.

At laparotomy, a nodular mass in the splenic flexure was found and biopsied. Above this mass was a larger fluctuant mass from which 800 ml of pus was drained. The biopsy showed poorly differentiated adenocarcinoma of colon. There were no immediate postoperative complications but the patient suffered a cardiac arrest on the third hospital day and died on the ninth hospital day.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

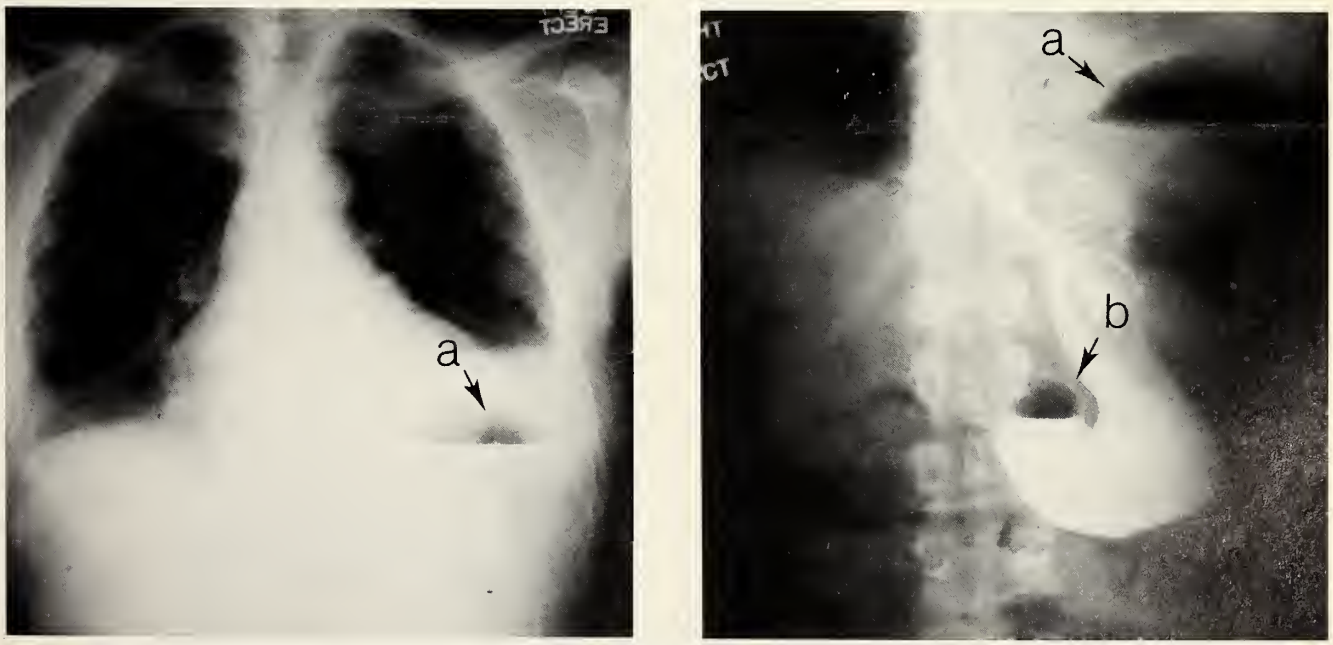


Figure 1. *Left panel shows bilateral pleural effusions, elevated left hemidiaphragm and a normal appearing stomach bubble (a). Right panel shows left subphrenic abscess (b) distinct from stomach.*

Discussion

The upper abdominal abscess is a life-threatening infection with a mortality approaching 30%.[1] In one study, 78% of cases of abdominal abscess occurred following abdominal surgery; the remainder were associated with perforated viscus.[1] Radiologic diagnosis is very important in these cases because so many of them are non-specific on presentation. In our patient, the abscess was not noted on initial examination of the plain films even though there were several radiologic clues that suggested the presence of a left subphrenic abscess.

Well-known radiographic features associated with subphrenic abscess include unilateral or bilateral pleural effusions, elevated hemidiaphragm and decreased diaphragmatic movement.[2] The abscess itself may appear as a soft-tissue mass or, characteristically, as an air-fluid level. Differentiation of normal stomach or bowel from an intra-abdominal abscess may be difficult. In a recent review of 58 patients with upper abdominal abscess exhibiting extraluminal gas or soft-tissue mass on plain film, 16 were initially missed, including one case simulating a stomach bubble.[1] Abscess in the left upper quadrant is more difficult to identify because of the presence of the stomach and colon, as illustrated in our case. An air-fluid level that extends laterally to the chest wall or medially across the midline[3] is likely to represent abscess rather than stomach. The absence of rugal folds in a left upper quadrant air-fluid level likewise suggests abscess. Finally, if old films are available, the persistence of an unchanging "stomach bubble" should suggest the possibility of subphrenic abscess.

Once the suspicion of abscess exists, further investigation is warranted. The increased penetration of an abdominal film may reveal a double gas-fluid level or a soft-tissue mass. A repeat plain film following nasogastric suction or the introduction of air or saline into the stomach may identify extraluminal gas distinct from stomach. The simple and underutilized upper GI series is an extremely effective method for identifying abdominal abscesses. This study may reveal extravasation of contrast, distorted bowel anatomy or extraluminal gas. Finally, abdominal CT scan and ultrasound are both highly accurate in demonstrating abdominal abscess. The CT scan not only is sensitive (96%) and specific (87%),[4] but also can provide detailed preoperative anatomy.

The key to the diagnosis in our case, however, was a suspicious and skeptical mind, not multiple radiographs. Clues that may be present on a plain film cannot be seen unless looked for with a critical eye.

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When Is a Drug Side Effect a Therapeutic Effect?

Edward L. C. Pritchett, M.D.

THE calcium channel blocking drugs like verapamil form an important new therapeutic class. These agents exert their therapeutic effects on supraventricular tachycardia by slowing atrioventricular nodal conduction and exert their therapeutic effect on angina by dilating arteries. Intravenous verapamil is extremely potent in terminating paroxysmal atrial tachycardia (figure 1) and in slowing the ventricular rate in atrial fibrillation and atrial flutter.

What, then, would we expect to see on the electrocardiogram of a patient taking oral verapamil who was in normal sinus rhythm rather than in a supraventricular tachycardia?

From the Department of Medicine, Duke University Medical Center, Durham 27710.

Slowing nodal conduction is manifested on the scalar electrocardiogram as a prolongation of the PR interval while heart rate, QRS morphology, ST segment, and T waves remain unchanged. We would, therefore, expect to see PR interval prolongation in a patient taking oral verapamil; it is an *expected* drug effect. PR interval prolongation is a measurable marker of drug activity. It provides reassurance that the patient is taking his drug and that the drug is being absorbed. Importantly, prolongation of the PR interval is not a criterion for reducing the dose or discontinuing the use of verapamil. In extremely rare cases, a patient may develop Mobitz type I 2° atrioventricular block (Wenckebach); only then does the drug effect become a true side effect and a reason to reduce drug dose.

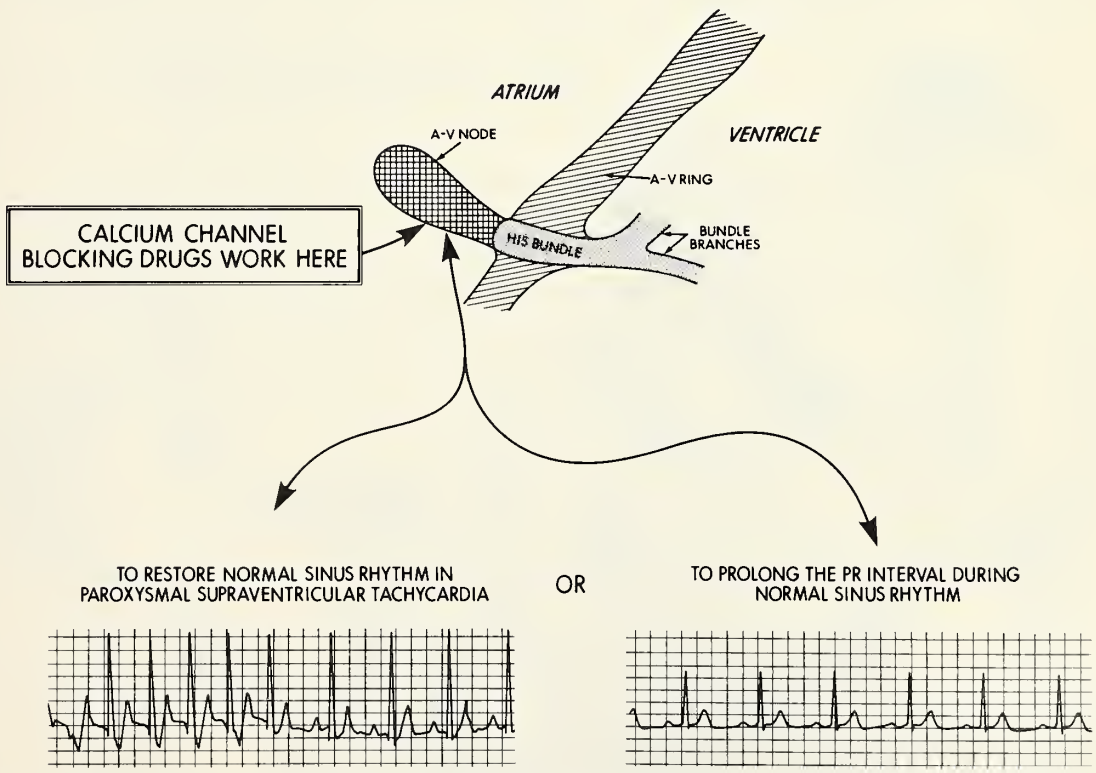
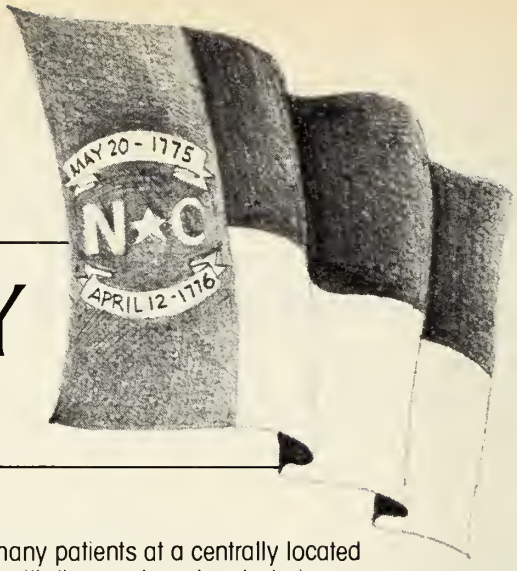


Figure 1. *Atrioventricular nodal conduction is markedly slowed by verapamil. This effect leads to termination of paroxysmal atrial tachycardia (left electrocardiogram) and to prolongation of the PR interval during sinus rhythm (right electrocardiogram).*

Roche salutes
the history of North Carolina medicine



THE 18-HOUR-A-DAY DOCTOR

Dr. Gaine Cannon

A modern-day version of the country doctor on horseback, Dr. Gaine Cannon covered his scattered practice around the Blue Ridge Mountain country near Balsam Grove, North Carolina, in a four-wheel-drive Jeep wagon.[1]

On an average working day, Dr. Cannon rose at sunup to see patients at his converted-farmhouse clinic before setting out to make his usual 15 to 20 house calls around the countryside. Generally, after treating his primary patient, he saw each member of the family as well—his personal effort at preventive medicine.

Multiple services

With the nearest hospital some 60 miles away and no pharmacy closer than an hour-and-a-half drive, Dr. Cannon filled his own prescriptions, delivered babies and treated many patients at a centrally located general store with the most modern techniques and medications. After a day on the road—usually within a 50-mile radius—Dr. Cannon's office hours would begin at 5:30 p.m. and stretch on until the last patient was attended to. His record-keeping sessions routinely filled the hour before midnight—rounding off Dr. Cannon's 18-hour day.

At all hours

But emergencies often interrupted his sleep. Dr. Cannon claimed his real office hours were 24 hours a day, and his patients revered him for it.

Dr. Cannon died in 1966 at the age of 68. He will be long remembered—most especially by the more than 5000 North Carolinians he helped bring into the world, some of them at the side of a rutted country road.

Reference: 1. Doctor in the backwoods, in Lee RV, Elmerl S *et al*: *The Physician.* New York, Life Science Library, Time Inc., 1967, pp. 38-50



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ROCHE

When the history reveals mixed depression and anxiety...

For the estimated 70 percent of nonpsychotic depressed patients who are also anxious,[1] Limbitrol provides both amitriptyline, specific for symptoms of depression, and the effects of Librium® (chlordiazepoxide HCl/Roche), the tested and dependable anxiolytic. Limbitrol is, therefore, a better choice for these patients than dual agents that contain a phenothiazine, a class of antipsychotic drugs which has been associated with tardive dyskinesia.

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Limbitrol also has a rapid onset of action which may lead to greater patient compliance. In a multicenter study, patients taking Limbitrol experienced 62% of their overall improvement within the first week of therapy.[2]

In another multicenter study,[3] the following symptoms associated with anxious depression were significantly reduced during the first two weeks of therapy:

- ☐ Headache—79%
- ☐ Early insomnia—91%
  Middle insomnia—87%
  Late insomnia—89%
- ☐ Gastrointestinal upset—73%

In two multicenter studies, only 1.9% of Limbitrol patients experienced cardiovascular side effects.[3]

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness such as operating machinery or driving a car.

References: 1. Rickels K: Drug treatment of anxiety, in *Psychopharmocology in the Proctice of Medicine,* edited by Jarvik ME; New York, Appleton-Century-Crafts, 1977, p. 316. 2. Feighner JP *et al: Psychopharmocology 61:* 217-229, Mar 1979. 3. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

In moderate depression and anxiety

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see summary of product information on following page.

LIMBITROL® Tablets Ⓥ Tranquilizer–Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100; Prescription Paks of 50.

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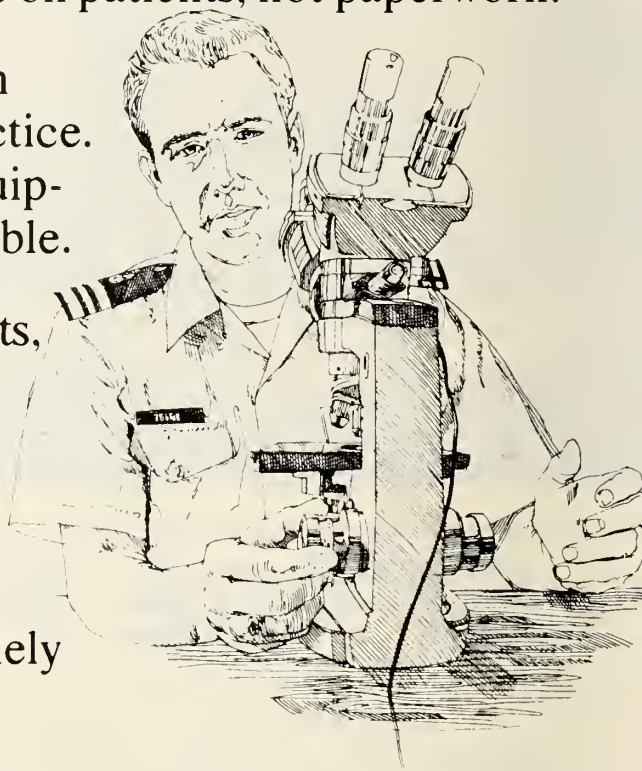
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- ☐ Hydrophilic (water-soluble) CORGARD does not readily cross the blood-brain barrier and is likely to cause fewer CNS side effects than lipophilic agents

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*This fixed combination drug is not indicated for initial therapy of hypertension. It may be appropriate if the fixed combination represents the dosage as titrated to the individual patient's needs.

†Please see brief summary of prescribing information on the last page of this advertisement for a discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS and WARNINGS, including avoidance of abrupt withdrawal.

ONCE-A-DAY CORZIDE®

Nadolol-Bendroflumethiazide Tablets

An important advance in Step-2 antihypertensive therapy

For brief summary please see next page.

ONCE-A-DAY CORZIDE®

Nadolol-Bendroflumethiazide Tablets

SQUIBB

An important advance in Step-2 antihypertensive therapy

CORZIDE® 40/5
CORZIDE® 80/5
Nadolol-Bendroflumethiazide Tablets

DESCRIPTION: CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration combines two antihypertensive agents CORGARD® (nadolol), a nonselective beta-adrenergic blocking agent, and NATURETIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide

CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS) **Bendroflumethiazide** — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs

WARNINGS: Nadolol — **Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — **Nadolol** — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and G.I. disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, *Bendroflumethiazide*, and PRECAUTIONS, *General, Bendroflumethiazide).*

Drug Interactions — Nadolol — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents. **Anesthetics, general** — exaggeration of anesthetic-induced hypotension (see WARNINGS, *Nadolol, Major Surgery).* **Antidiabetic drugs (oral agents and insulin)** — hyperglycemia or hyperglycemia, adjust antidiabetic drug dosage accordingly (see WARNINGS, *Nadolol, Diabetes and Hypoglycemia).* **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect, monitor closely for evidence of hypotension and/or excessive bradycardia.

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics. **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of antidiabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or peripheral adrenergic blocking drugs** — potentiated effect. **Preanesthetic and anesthetic agents** — effects may be potentiated, adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, *General, Bendroflumethiazide).*

Carcinogenesis, Mutagenesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed.

Pregnancy — **Teratogenic Effects** — **Nadolol** — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose, no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus; these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol-Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients, paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash, pruritus, headache, dry mouth, eyes, or skin, impotence or decreased libido, facial swelling, weight gain, slurred speech, cough, nasal stuffiness, sweating, tinnitus, blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol. The following adverse reactions may also occur: **Central Nervous System** — reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis, ischemic colitis. **Hematologic** — agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat, laryngospasm, respiratory distress. **Miscellaneous** — reversible alopecia, Peyronie's disease, erythematous rash, arterial insufficiency.

Bendroflumethiazide — **Gastrointestinal System** — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersensitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed. Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, employ the following measures, as appropriate. **Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation. **Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a $beta_2$-stimulating agent and/or a theophylline derivative. **Stupor or Coma** — Supportive therapy as warranted. **Gastrointestinal Effects** — Symptomatic treatment as needed. **BUN and/or Serum Electrolyte Abnormalities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

May 10-11
Infectious Disease Update 1984
Place: Greensboro
Fee: $75
Credit: 11 hours Category I AMA
Info: Fred Levick, Greensboro AHEC, 1200 North Elm Street, Greensboro 27401. 919/379-4025

May 10-12
North Carolina Chapter of the American College of Surgeons
Place: Boone
Info: Richard W. Furman, M.D., 702 State Farm Road, Boone 28607. 704/264-2340

May 16
Progress on Type 2 Diabetes
Place: Raleigh
Fee: None
Credit: 3 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 17
Records and Other Necessities
Place: Asheville
Info: Wayne Parker. 919/828-9334

May 17-18
Social Behavior in Autism
Place: Chapel Hill
Fee: $25 in-state; $100 out-of-state
Credit: 12 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 17-19
Floyd W. Denny Alumni Lecture Series
Place: Chapel Hill
Info: Gerald W. Fernald, M.D., Pediatrics, 509 Burnett-Womack Bldg. 229H, UNC School of Medicine, Chapel Hill 27514. 919/966-2085

May 18-20
Pathokinesiology of Cerebral Palsy
Place: Chapel Hill
Info: Darlene S. Slaton, Physical Therapy, C 221H, UNC School of Medicine, Chapel Hill 27514. 919/966-4708

May 24
Records and Other Necessities
Place: Shelby
Info: Wayne Parker. 919/828-9334

May 25-26
13th Annual Seminar: Gut and Lung Problems in Pediatrics
Place: Durham
Credit: 12 hours
Fee: $60
Info: Alexander Spock, M.D., Box 2994 Duke University Medical Center, Durham 27710. 919/681-3364

May 25
Pediatrics Day
Place: Greenville
Credit: 7 hours
Fee: $55
Info: Mary C. Valand, Box 7224 ECU School of Medicine, Greenville 27834. 919/758-5200

May 31-June 2
The Sea Level Invitational Conference on Geriatric Medicine
Place: Sea Level
Info: M. Valand, ECU School of Medicine, PO Box 7224, Greenville 27834. 919/758-5200, ext 208

May 31-June 2
Approaches to Ethical Decision Making
Place: Durham
Info: Nettie Wilburn, UNC-CH School of Nursing, Carrington Hall 214H, Chapel Hill 27514. 919/966-3638

June
Sports Medicine Seminar
Place: UNC
Info: B. F. LeVeau, Physical Therapy, Wing C-221H, Chapel Hill 27514. 919/966-5005

June 1-2
Neurology for the Primary Physician
Place: Chapel Hill
Fee: $100
Credit: 11 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118.

June 5
Duke Tuesday
Place: Durham
Credit: 5 hours
Info: L. Mace, Urology, Duke U Med Center, Box 3707, Durham 27710. 919/684-2033

June 6-7
Fellows Symposium
Place: Chapel Hill
Info: John J. Frey, M.D., 231 MacNider Bldg 202H, Chapel Hill 27514.

June 17-22
Health Promotion — Wellness Institute
Place: Raleigh
Fee: $250
Credit: 30 hours
Info: NC Health Promotion, Wake AHEC, 3000 New Bern Ave, Raleigh 27610. 919/755-8018

June 20
Suicide by Poisoning
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St, Sanford 27330. 919/774-4100, ext 394

June 22-23
North Carolina Affiliate, American Heart Association, 35th Annual Meeting and Scientific Sessions
Place: Durham
Info: N.C. Heart Association, Chapel Hill 27514

July 9-14
26th Annual Postgraduate Course/Morehead Symposium
Place: Atlantic Beach
Credit: 25 hours
Info: C. Easterling, Duke U Medical Center, Box 3306, Durham 27710. 919/684-6485

July 18
Hospital Nutrition Update

Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St, Sanford 27330. 919/774-4100, ext 394

July 30-August 3

Diagnostic Imaging
Place: Atlantic Beach
Fee: $400; $250 if in training and with letter from chairman
Credit: 26 hours
Info: J. D. Wright, Box 3808 Duke Hospital, Durham 27710. 919/681-2711

August 4

Geriatric Education Day
Place: Raleigh
Credit: 4 hours
Info: NCAFP 919/781-6457

August 7

Malpractice Awareness — STAT
Place: Greensboro
Info: Wayne Parker. 919/828-9334

August 14

Malpractice Awareness — STAT
Place: Charlotte
Info: Wayne Parker. 919/828-9334

August 15

Electrolytes/Arterial Blood Gases/Fluid Balance
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St, Sanford 27330. 919/774-4100, ext 394

August 21

Malpractice Awareness — STAT
Place: Goldsboro
Info: Wayne Parker. 919/828-9334

OUT OF STATE

May 7-9

Gold Coast Seminar: Medicine
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306 Duke University Medical Center, Durham 27710. 919/684-6485

May 10-12

Current Concepts of Clinical Infectious Diseases
Place: Hot Springs, VA
Fee: $220, $165, $295
Credit: 13¾
Info: Gerald L. Mandell, M.D., Univ of Virginia, Charlottesville

May 18

A Seminar on Investigation of Sex Crimes
Place: Johnson City, Tenn.
Fee: $40
Credit: 8 hours
Info: Sue Hutchinson, Office of CME. 615/928-6426, ext 204

May 18-19

Practical Dermatology for the Non-Dermatologist
Place: Williamsburg, VA
Fee: $90
Credit: 7 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 24-27

8th Annual Radiology Symposium
Place: Hilton Head, SC
Fee: $350
Credit: 19 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 30-June 2

AACA 1984 Spring Seminar in Anesthesiology
Place: Hilton Head, SC
Info: Amer Academy of Clinical Anesthesiologists, P.O. Box 11691, Knoxville, TN 37939-1681. 615/588-6279

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine
Place: Sea Level, GA
Info: Mary C. Valand, CME, ECU School of Medicine, Greenville 27834. 919/758-5200

June 4-8

Cornell University Diagnostic Radiology Update Emphasizing Advances in Imaging and Interventional Procedures
Place: Bermuda
Credit: 100 hours
Fee: $400, $300
Info: Ann Wold, Gallagher/Wold, Inc., 420 Lexington Ave., New York 10170. 212/986-1277.

June 18-July 1

The Cancer Patient: Surgical Treatment and Rehabilitation
Place: Cruise Benice, Yugoslavia, Greece, Turkey, Russia
Info: C. Easterling, Box 3306 Duke Hospital, Durham 27710. 919/684-6485

June 27-30

Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Credit: 15.5 hours Category 1 AMA
Fee: $350
Info: Dermatology, Box 2987 Duke University Medical Center, Durham 27710. 919/684-6728

July 2-7

Midsummer Family Practice Digest
Place: Myrtle Beach, SC
Credit: 30 hours
Info: NCAFP. 919/781-6476

July 26-28

6th Annual Pediatrics Primary Care Conference
Place: Virginia Beach, VA
Fee: $275
Credit: 12 hours
Info: S. Rosner, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

New Members

ALAMANCE-CASWELL

Michael Joseph Dimeo (PUD), 80 Harper Building, 327 Graham-Hopedale Rd., Burlington 27215

Howard Edward Miller (ORS), 723 Edith Street, Burlington 27215

BEAUFORT-HYDE-MARTIN-WASHINGTON-TYRRELL

David Alan Desrochers (R), 608 E. 12th Street, Washington 27889

BUNCOMBE

Daniel Thomas Eglinton (ORS), #8 East Forrest Road, Asheville 28803

CARTERET

Viorica Elisabeth Tanase (PD), P.O. Box 220, Hubert 28539

CATAWBA

Douglas Worth Michael (FP), 305 First Street, East, Conover 28613

CLEVELAND

Michael Lynn Barringer (GS), 904 Meadowbrook Lane, Shelby 28150

Robert Dean Bayliss, Jr. (Student), 1641-G Northwest Boulevard, Winston-Salem 27104

Joel Miles Carter (ON), P.O. Box 340, Shelby 28150
Thomas Scott Ellison (Student), Northwest Boulevard, 1641-R Magnolia Apts., Winston-Salem 27104
Stephen Watson Jones (Student), P.O. Box 8453, Greenville 27834
Johnson Hall Kelly (Resident), 2706 Lullington Drive, Winston-Salem 27103
Vera Crooke Shanley (AN), 1520 E. Marion Street, Shelby 28150
Brian McCullough Strain (Resident), 2404 Longview Ave., Apt. 1-E, Roanoke, VA 24014

CUMBERLAND
John Anthony Brodston (GS), 3924 Foster Drive, Fayetteville 28301

DURHAM-ORANGE
Beverly Lynn Alston (Student), UNC, 556 Craige Dormitory, Chapel Hill 27514
Paolo Flezzani (AN), Dept. of Anesthesiology, Box 3071, Duke Medical Center, Durham 27710
Richard Henry Gibson (Resident), 97 Oak Leaf Lane, Chapel Hill 27514
Mary Linda Hawes (Resident), 111 Greenfield Road, Chapel Hill 27514
Nancy Melinda Hill (Student), 202 Pritchard Avenue, Chapel Hill 27514
Janine Corbitt Jones (Resident), 103 Creeks Edge, Box 62, Polks Landing Station, Chapel Hill 27514
Stuart Johnston Knechtle (Resident), P.O. Box 31156, Durham 27710
Thomas Lloyd Lambert (Student), Box 2813, Duke Medical Center, Durham 27710
Mark Harris Lerner (Student), Box 2744, Duke Medical Center, Durham 27710
James Randall Long (Student), 20 Brighton Square, Carrboro 27510
Patricia Ann Michael (Student), UNC School of Medicine, Chapel Hill 27514
Leonard R. Prosnitz (TR), Box 3275, Duke Medical Center, Durham 27710
Linda Marie Raines (Student), 39-H Laurel Ridge Apts., Chapel Hill 27514
Mitchell Dennis Shub (PD), UNC, Burnett-Womack Bldg. #310, Chapel Hill 27514
Ida Janice Deas Stratton (PD), Rt. #2, Box 435-A, Durham 27705
Jennifer Elaine Taylor (AN), Box 3061, Duke Medical Center, Durham 27710
Willard David Wilcox (OPH), 911 Broad Street, Durham 27705
William Walter Woodruff, III (Resident), Box 3286, Duke Medical Center, Durham 27710

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Richard Eli Hedrick, Jr. (OBG), 2909 Maplewood Avenue, Winston-Salem 27103
Elizabeth Rankin Vaughan (EM), 8058 Deverow Court, Lewisville 27023

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Timothy Pius Gibble (IM), 1015 Professional Village, Greensboro 27401
David Barnett Massey (Resident), P.O. Box 18227, Greensboro 27419
Stanley Neal Tennant (IM), 530 N. Elam Avenue, Greensboro 27403
Gerald Lynn Truesdale (PS), 1114 Magnolia Street, Greensboro 27401

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Joseph Nelson Vanderwerf, 306 Woodland Trail, Hendersonville 28739

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Mitchell Crawford Reese (PD), 555 Carthage Street, Sanford 27330

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Richard William Croskery (Resident), 704 Willow Street, Greenville 27834
Abbas Emami (PHO), 208 Joseph Street, Greenville 27834
George Klein (Resident), Doctor's Park Apts. #K2, Greenville 27834
Charles Leonard Knupp (IM), 1042 E. Rock Spring Road, Greenville 27834
Todd Lowell Sobol (Student), 108 S. Harding Street, Greenville 27834
Roger Edmund Thomas (FP), Dept. of Family Medicine, ECU School of Medicine, Greenville 27834

POLK
Thomas Christopher Perraut (OPH), 244 Pacolet Street, Tryon 28782

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Robert Baird Scott (FP), 132-A W. Miller Street, Asheboro 27203

ROBESON
Richard Arthur Roski (NS), 202 W. 27th Street, Lumberton 28358

SURRY-YADKIN
Richard Lowell Bartsh (FP), P.O. Box 988, Mount Airy 27030

UNION
Joseph John King, Jr. (ORS), 870 Sunset Drive, Monroe 28110

WAKE
Louis David Allen (PD), 3001 Essex Circle, Raleigh 27608
Rekha Jain (IM), 5813 North Boulevard, Raleigh 27609
David Clifton Powell (GS), 1108 Dresser Court, Raleigh 27609
Roger Bivins Russell (PS), Cameron Village, 233 Bryan Building, Raleigh 27605
Barry Neil Straus (AN), 2609 Kingsley Road, Raleigh 27609

WATAUGA
Luis Nicholas Hernandez (AN), P.O. Box 1493, Boone 28607
Arnold Oliver Welden (FP), 124 Wildwood Lane, Boone 28607

WAYNE
Richard James House (OTO), 1207 E. Holly, Goldsboro 27530

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In Memoriam

Hans Lowenbach, M.D.

The North Carolina Neuropsychiatric Association lost a long standing Fellow and dear friend when Dr. Lowenbach passed away quietly in his home on October 19, 1983. He served as delegate to the Assembly of District Branches and was president of the North Carolina District Branch (NCNPA) in 1963.

Hans was born on January 31, 1905 in Duisburg, Georgia. He had his medical education at the University of Hamburg and had his internship and part of his residency in Germany with some of his studies being at the Kaiser Wilhelm Brain Research Institute in Berlin. He completed his psychiatric training at the Phipps Psychiatric Clinic of the Johns Hopkins Hospital in Baltimore, Maryland. He was among the first faculty members of the Department of Psychiatry at Duke University in 1940. He served in the U.S. Army Reserve in 1949-1951 and then became Commander of the U.S. Army Reserve Unit in Durham, North Carolina until his retirement as Colonel in 1969. He was a Professor of Psychiatry at Duke University and had over sixty publications. Hans became known as a distinguished teacher and role model for medical students and psychiatric residents. After his retirement from Duke University in 1975, he continued his contact with students and training until 1982. He was respected by all who were privileged to know him as students, trainees and peers because of his fairness, expertise in evaluation of the patient and dedication to teaching. His wisdom, warmth, and tolerance for his fellow man will be missed by all of us who knew him.

Dr. Lowenbach is survived by his wife, Eileen Sullivan Lowenbach; three daughters, Christine Shore of Portland, Oregon, Torry Lowenbach of Toronto, Canada and Trude Lawrence of Atlanta, Georgia; and two sisters, Hilda Lowenbach and Trude Lowenbach, both of Dusseldorf, West Germany. The family has requested that those wishing to contribute to Hans' memorial send contributions to Dr. Hans Lowenbach Memorial Fund, Box 3701, Duke University Medical Center, Durham 27710.

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Letters to the Editor

Affective Sickness

To the Editor:

Dr. Freedman's observations (*NCMJ* 45:155-156, March 1983) of the signs and symptoms of depression agree, in most part, with those accepted by the American Psychiatric Association. He obviously is an observing and concerned physician, so I find it incongruous that he states that ". . . the treatment is not that of persons but rather of their neurochemical processes." Would it not be best to treat the person and the neurochemical process simultaneously? Does Dr. Freedman truly believe that "detailed personal histories are not needed . . .?"

James L. Mathis, M.D.
Department of Psychiatric Medicine
East Carolina University
Greenville 27834

Hematologists 1, Cardiologists 0

To the Editor:

I was rather surprised at last week's Medical Conference to have one of Duke's erudite cardiologists attribute the discovery of the physical findings of aortic insufficiency to D. J. Corrigan. Dr. Thomas Hodgkin published a good account of aortic insufficiency three years before Corrigan wrote about it. The paper, entitled "On Retroversion of the Valves of the Aorta," appeared in the *London Medical Gazette* on March 7, 1829. Corrigan's paper was published in 1832. The following two quotations are from the paper by Hodgkin:

> Thou wilt probably recollect having pointed out to me, a few months ago, a particular state of the valves of the Aorta, which, by admitting of their falling back towards the ventricle, unfits them for the performance of their function. The specimen . . . was first observed by thyself, exhibits this derangement in a well-marked manner.

In defining the antemortem findings he noted that

> In diseases of the aortic valves, auscultation often detects a prolonged and perverted sound, such as has been compared to the stroke of a saw, the puff of a pair of bellows or the action of a rasp.

R. Wayne Rundles, M.D.
Department of Medicine
Duke University Medical Center
Durham 27710

Editor's reply: This hematologist can see beyond the blood cells.

The Extinct Physician: Heads

To the Editor:

I now read the *Journal* from cover to cover. Thanks so much for the new and interesting format.

Dr. Hadler's article on "The State of Medicine in 1983: The Extinction of the Physician" in the February 1984 *Journal* was one of the most instructive I have yet read on the present state of the practice of Medicine everywhere.

As an old friend and distinguished colleague of mine has always said, "What this patient needs is a Doctor!"

Patients still respond to kindness, listening, being seen at the time of their appointments, personal unhurried attention, history or interval note taking by their doctor, reasonable fees and thorough physical exams when seen at the office or hospital.

Joseph B. Stevens, M.D.
1017 Professional Village
Greensboro

The Extinct Physician: Tails

To the Editor:

The article "The State of Medicine in 1983: The Extinction of the Physician" by Nortin M. Hadler, M.D. of the Department of Medicine and Microbiology, University of North Carolina School of Medicine, seems to exemplify its own problem: i.e., the ivory tower isolation of medical school educators whose attitudes are unrelated to reality and who are often unaware of the trends of American medicine.

The author is apparently uninformed of his own institution's efforts in producing not just "primary care internist-pediatrician" clinicians, but scientifically based, intellectually stimulated, patient-oriented and caring family physicians. The article to me is ten years behind the response of the legislature and the general public in demanding and now in receiving well-trained, compassionate, people-oriented physicians.

"An ill individual may still turn to and value his physician." Family physicians are "skilled," "highly trained" and "scientific" and they can and are "expected to help patients cope with the impact of their disease in their life."

True, "minions have been cultivated to supplement the doctor" but to supplement, not supplant. The ethic that all physicians should live by is "You can't learn it all, but you can never cease trying," for as I was taught at Duke twenty years ago, "half of all you learn today will be later proven untrue, but I cannot tell you now which half this will be."

In 1974 this article would have been a foresighted observation; the academic community's attitudes still remains ten years behind. The social realities are that the public wants, needs and demands such physicians. Family Medicine is responding to this call. Your elegy for the "health care system" in America is not appropriate and issued too late.

The isolated, investigative academician is the only one who cannot identify "a niche, need or role for a personal physician any more."

America is maintaining a cadre of providers of health

care. They are the primary care internists, pediatricians, and family physicians.

Harry H. Summerlin, Jr., M.D.
944 Tunnel Road
Asheville 28805

Another Man's Poison

To the Editor:

As an old hand in this "poison stuff," I find Ronald Mack's *Toxic Encounters* both informative and hilarious.

Jay M. Arena, M.D.
Duke University Medical Center
Durham 27710

Emergency Use of Epinephrine Restricted

To the Editor:

In regard to a recent letter to the editor (*NCMJ* 45:137-138, February 1984) regarding non-physicians who have been trained to administer epinephrine in emergency situations, I believe it should be called to the attention of your readers that North Carolina General Statute 90.143-509 permits the Board of Medical Examiners to approve individuals who have successfully completed appropriate training programs to administer epinephrine to persons who suffer a severe adverse reaction to **insect stings only.** The statute goes on to restrict such an administration only "in the absence of the availability of physicians or other practitioners who are authorized to administer the treatment."

A. T. Pagter, Jr., M.D., President
North Carolina Board of Medical Examiners
Raleigh 27601

Corporate Restructuring

To the Editor:

I have had occasion to read the January 1984 issue of the *North Carolina Medical Journal,* and particularly the article by Paul M. Wiles on "Corporate Restructuring: One Answer to TEFRA's Challenge."

I was most impressed with the quality of the article and with the excellent manner in which Mr. Wiles addressed the issues. I know that there are several different ways in which hospitals can restructure, but certainly the reasons and benefits are clear and Mr. Wiles describes them well.

An interesting situation has occurred over the past two to three years, and that has been the need for hospitals to reconsider restructuring that was accomplished in 1981 and 1982 to bring the organizational arrangements in line with the Tax Equity and Fiscal Responsibility Act, and in particular with the changes in the type of competition that exists. For example, our institution went through a restructuring in late 1981 and early 1982, but has felt the need now in late 1983 and 1984 to re-evaluate our initial methodology and ensure that the organizational structure reflects best the changes in the marketplace.

I agree wholeheartedly with the need for professional consultation and especially heavy involvement of many members of the board and medical staff. Hospitals that ignore the concerns and issues that the medical staff bring up will find that the corporate restructuring is counterproductive rather than an aid to them as they move through the challenging times ahead.

I look forward to reading more articles on such critical issues in your journal.

Robert F. Burgin
President
Memorial Mission Hospital
Asheville 28801

Warts and All

To the Editor:

The response to our article on warts published in the *North Carolina Medical Journal* (44:730, November 1983) has been overwhelming. The article was picked up by the various news agencies and apparently circulated throughout the United States.

Wart sufferers from Georgia to Hawaii have written with their own personal experiences with warts and have suggested cures that even Dr. Callaway had never heard of. It is evident from these letters that patients enthusiastically support the notion that the power of suggestion is efficacious not only in wart therapy but in medical care in general.

From the response I have received I am of the opinion that warts are one experience that unites all mankind. An experience with warts is something we all have in common.

I am enthusiastically collecting the suggestions from your readers. The papaya seeds from Hawaii, the bee pollen from Georgia, the magic stone from New York, and many other remedies are being carefully saved for posterity. I would love to hear from anyone who has a treatment they think we should know about.

Claude S. Burton, M.D.
VA Medical Center
Durham 27705

From the Committee on Communications

To the Editor:

The blue section in the October 1983 issue of the *NCMJ* regarding resources for the visually impaired has stimulated the Committee on Communications to expand its scope.

We are exploring the feasibility of producing the Society's educational pamphlets for the public in braille. We hope to encourage the N. C. Pharmaceutical Association to make prescription labels in braille available in most cities.

Physicians in private practice should encourage visually impaired to place their medications in boxes divided into compartments to facilitate taking drugs on a daily/weekly basis accurately. These simple homemade devices can be fashioned to suit the individual needs of each patient.

We welcome additional ideas from our colleagues; please forward them to our Communication Director, Tom Bennett, at Society headquarters.

Elizabeth P. Kanof, M.D.
Chairman, Committee on Communications
North Carolina Medical Society
Raleigh 27611

From the Managing Editor:

I would like to share some good news. For the first time since I've been Managing Editor of the *North Carolina Medical Journal* the revenue from national and local advertising will cover the cost of composing, printing, and binding this issue of the *Journal*. I hope each of you will remind your friends that the *Journal* is an effective advertising medium and mention the *Journal* when you deal with any of our present advertisers.

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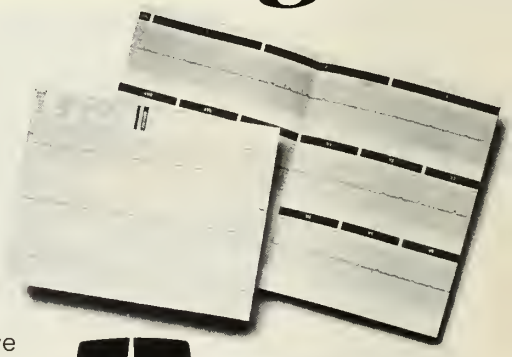
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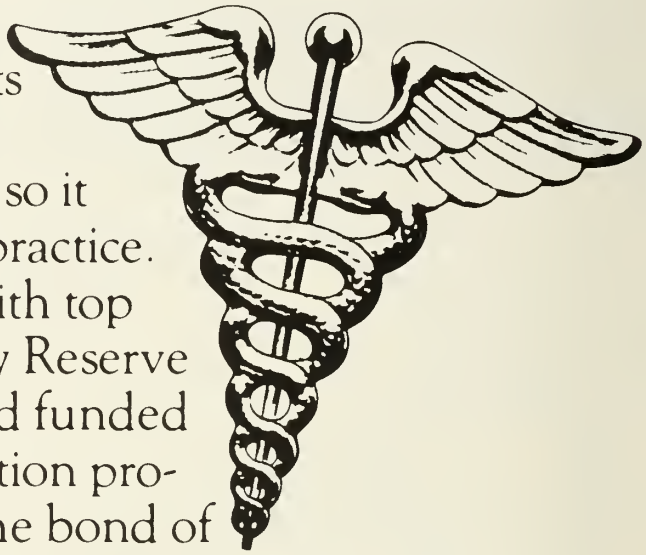
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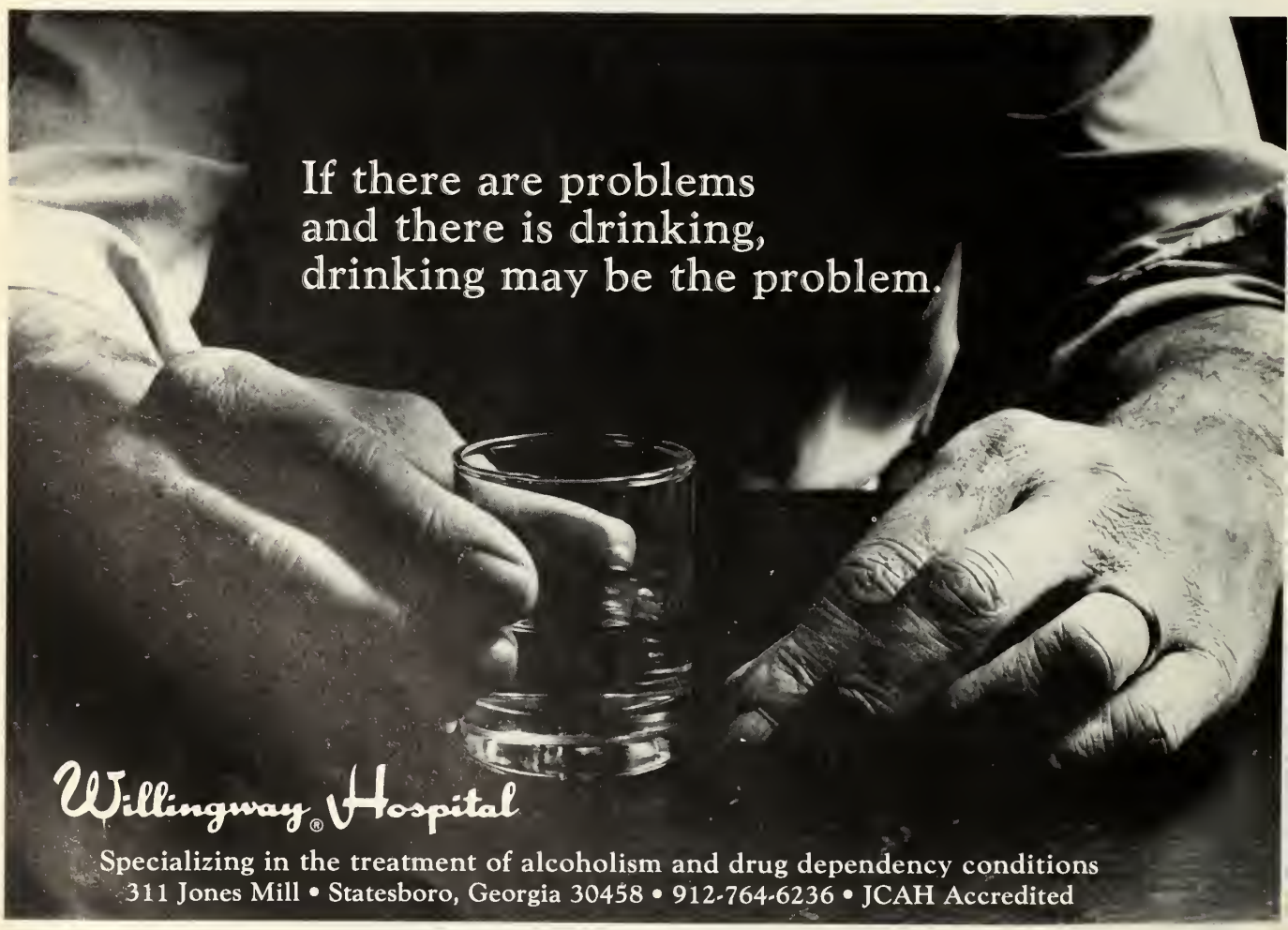
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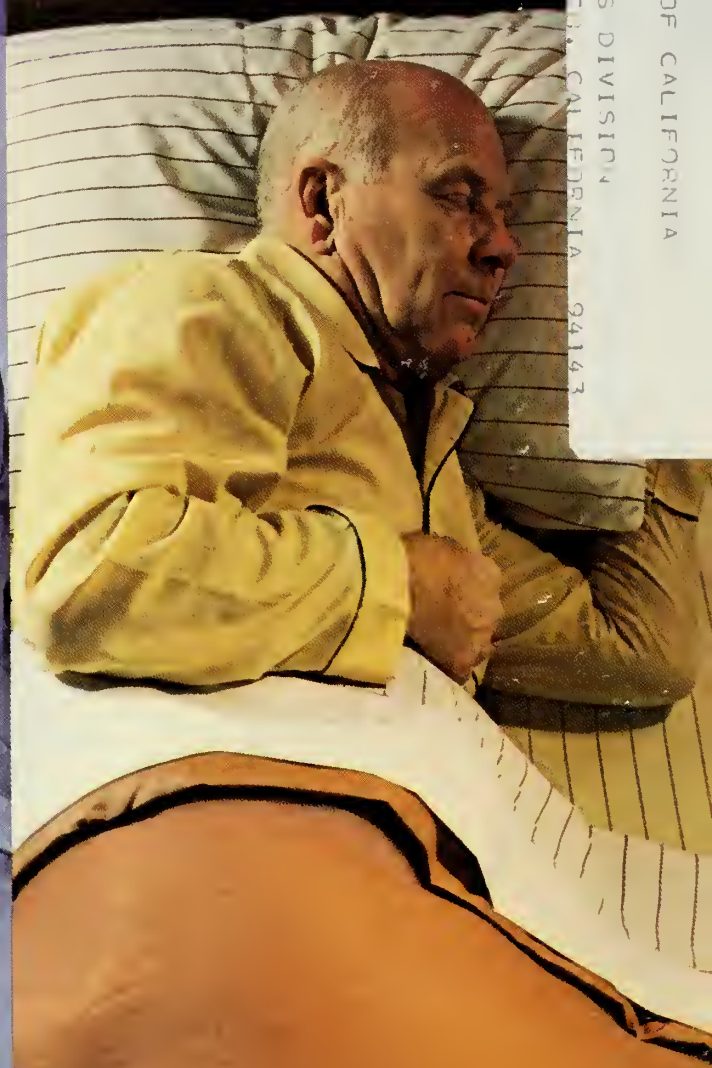
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Official Journal of the NORTH CAROLINA MEDICAL SOCIETY June 1984, Volume 45, No. 6

Black Dermographism by Lester Fahrner, M.D., page 395

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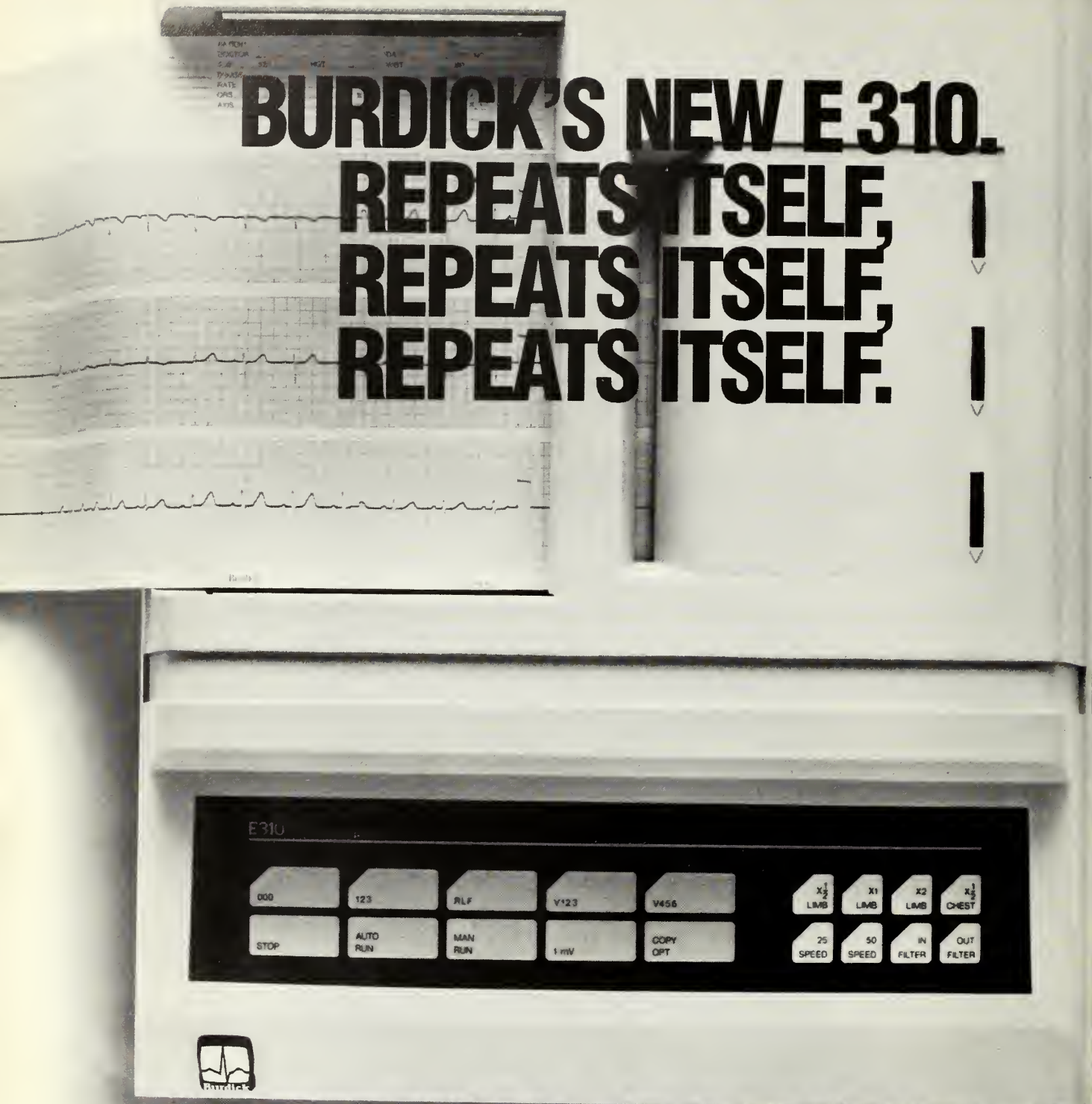
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SCIENTIFIC ARTICLE

Renal Dialysis for Kidney Failure in North Carolina: History, Practice, and Lessons

Robert A. Gutman, M.D.

RENAL failure entitles a patient to federal funds for his therapy with only one provision, that he or a member of his family has participated in our Social Security system. Since the law providing this entitlement was passed, the number of dialysis patients in the United States has grown from approximately 7,000 to over 70,000. With this population surge, costs have gone from about 0.5 billion to nearly 3 billion dollars per year. Kidney failure is the only disease for which there is an unrestricted entitlement to care in the general community.* No other chronic disease is similarly covered: not liver failure, advanced heart disease, leukemia, sickle cell anemia, cerebral palsy, cancer, stroke or myocardial infarction. In all other instances, entitlement to government medical assistance is based on the individual's present or past role in society. For example, persons over age 65, military personnel and their dependents, veterans, Indians, Merchant Marines, postal workers, and many who are recipients of welfare programs are covered by one or another form of federal or state medical insurance. The End-Stage Renal Disease (ESRD) Program provides treatment for a single catastrophic disease and may be a harbinger of programs to come, possibly including liver and heart transplantation and replacement of Factor VIII for hemophiliacs.

In North Carolina this unique federal program has some of its own distinguishing characteristics. For example, the North Carolina End-Stage Renal Disease Program differs from that of our neighbors by being more cohesive, by involving patients to a larger degree, and by its freedom of control from outside large-chain dialysis companies. In this article I shall trace the political origins at both federal and state levels of our program and give my interpretation of what lessons are extractable from our experiences. The story is interesting because it contains features of possible future government involvement in large-scale funding for other catastrophic diseases, yet the experience is small enough to be told in some detail.

An early warning to the reader is warranted. Only those individuals on either political extreme will be able to extract a single crisp, clean lesson in this account. For those with an unqualified commitment to full financial assistance for medical therapy, the government's program will seem tentative, half-hearted, and unnecessarily complex. On the other hand, those who view government medicine as an anathema will view the cost overrun and the crippling entitlement expansion as a clear vindication of their principles.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

* Venereal diseases carry disease-specific entitlement, but they are generally acute illnesses and care is free only at specific sites, such as community health centers. Leprosy and tuberculosis entitle a patient to care only at government institutions.

Origins of the Program

Hemodialysis is nothing new. During the Nazi occupation of Holland, Dr. Willem J. Kolff successfully developed a system for pumping blood through an outside-the-body circuit. The lengths of tubular semipermeable cellophane were actually German sausage casing. Kolff brought his apparatus to the U.S. before 1950, and within a few years clinical hemodialysis became a practical method of treating acute renal failure. But the revolutionary character of hemodialysis began only around 1961 when Dr. Belding Scribner demonstrated the feasibility of continuous maintenance dialysis. Originally, the treatments cost approximately $30,000 (1962 dollars) per year. The early patients were relatively young and had no problems except kidney failure; indeed, of the first three patients chosen in 1960 for these experimental procedures, two lived more than 10 years and one is alive today. Although Scribner realized that his achievement raised difficult social issues, he began early in the technologic development to seek equitable forms of funding. In sharp contrast, some prominent members of the academic nephrology community expressed grave doubts about the wisdom of proceeding with any government funding. They likened this therapy to the iron lung and its use for poliomyelitis victims: a "halfway therapy." Suggesting that the money would be better spent on research, they made an oversimplified analogy to the successful development of polio vaccine, which had virtually eliminated the need for iron lungs. So it would be with kidney research, they claimed; soon dialysis machines would not be necessary.

But the forces of human nature were at work. Seattle began to raise money for a few of its citizens and by 1962 the personal dilemma of choosing which candidates would receive the scarce funds was sensationalized by *Life* magazine. Money from the federal government began to trickle in shortly after that, first through the establishment of

Veterans Administration Centers in 1963, and next through the establishment in 1964 of demonstration projects under the Public Health Service. From 1964 to 1967, these demonstration projects were by and large successful. Patients were living longer and some even were returning to work.

The United States was already on the slippery slope of granting nearly universal entitlement to government funds for dialysis, with transplant therapy soon to be included. The first five years of this evolution were quiet. Although U.S. Senator Henry Jackson (D-Wash) proposed expansion of the program on several occasions, neither the House nor the Senate took action until 1969. First, Congress expanded the role of the Regional Medical Programs to include kidney disease as well as cancer, heart disease, and stroke. Under this legislation, the Public Health Service provided funds for community dialysis centers. Shortly after that, Congress began to hear testimony from relatively healthy patients, one of whom actually carried out a home dialysis treatment in a congressional hearing room. Important senators such as Jackson (and later, Vance Hartke) assured their fellow lawmakers that money for dialysis and transplantation would be recouped easily by virtue of the savings of welfare payment to families of rehabilitated patients. Consequently, Congress passed legislation in 1972 entitling Social Security participants and their families 80% support for treatment for end-stage renal failure when "medically determined" to be necessary. The character of the program immediately began to change. Medical determination became simply "making the diagnosis of kidney failure." Under the relatively generous reimbursement policies set out at that time, commercial competition flourished and the actual cost of treatment began to fall, leaving room for large profits for commercial operators. Large-chain companies came into existence, some seemingly overnight. The machines, the dialyzers, the disposable equipment and much of the associated technology improved considerably under the dual stimuli of federal money for research and federal money for services. The dominant characteristics of the patients in the program began to change dramatically as older and sicker patients with the diagnosis of end-stage renal disease were admitted.[1] These patients had many other medical problems in addition to renal failure.

North Carolina Developments

Here in North Carolina the end-stage renal program had already acquired a unique character. Before the passage of the 1972 Social Security legislation, leaders of the nephrology training programs at Duke and the University of North Carolina worked closely with key members of the North Carolina legislature. As a result of their efforts, aided considerably by a prominent legislator who was himself a renal failure patient, seed money was set aside to aid patients with the costs of home dialysis or transplantation. This money prompted the development of a "renal office" in the State Department of Human Resources which relied heavily on the professional advice of prominent nephrologists in academic medicine and in clinical practice. Statewide cooperation in planning and patient assistance emerged from these efforts so that when the federal program appeared, North Carolina already had the mechanism to deal with the new rules and the new money.

For example, Congress determined that the nation should be divided into 32 End-Stage Renal Disease networks, each network to consist of all the providers of dialysis and transplantation services within its defined boundaries. The reason for establishing networks was to provide local Professional Services Review Organization-styled systems for monitoring the quality and cost of therapy. In many instances, the geographical boundaries of a network were to include more than one state or several pieces of several states. Thanks to our early preparations and our leadership, North Carolina, originally designed to be divided among two networks, was finally made a network of its own, thus avoiding confusion and overlapping areas of responsibility. Consequently, our network (No. 21) assumed many of the advisory functions previously reserved for the State Department of Human Resources including important roles in planning the location and character of treatment centers during the first years. This *advisory function* became more important for many physicians and patients than the *quality assurance functions* which the federal government expected to dominate. Our tradition of cooperation held as new facilities opened under the guidance of our state's program directors, some of whom were graduates of training programs at Duke and UNC. Owing to circumstances, example, and planning, most of the North Carolina units became owner-operated rather than franchise operations for large-chain dialysis companies. In other parts of the country, most of these large companies (some "profit" and some "non-profit") had developed Center dialysis to the near exclusion of home treatment options. By contrast, most of the owner-operators of the North Carolina dialysis programs have used these options for fully a fourth of their patients. North Carolina has been the third or fourth most frequent user of home dialysis on a per capita basis and yet has one of the largest fractions of "for-profit" dialysis units — giving lie to the premise that for-profit dialysis led inevitably to overuse of the Centers and larger profits. More recently, the government has removed virtually all financial advantage for in-Center dialysis. This will have little impact in North Carolina because of the pre-existing rate of home dialysis usage.

Current Practices

By 1978 the present dominant characteristics of the federally funded End-Stage Renal Disease Program were becoming clear. Universal funding and diagnosis-determined entitlement were being translated into an increased willingness to use dialysis or transplantation even for patients with far-advanced age and other illnesses. The average age of patients on dialysis was rising, as it continues to rise, by nearly one year with each passing year of the program. The number of new patients starting dialysis was therefore rising also; new patients in 1978 were about 60 per million versus the current rate of well over 80 per million. Another feature to emerge was the uneven distribution of patients among the different communities. Because of the striking predominant risk of end-stage renal disease among Blacks (figure 1), communities with a large fraction of Black citizens had far more patients than did other communities. Today, these communities are

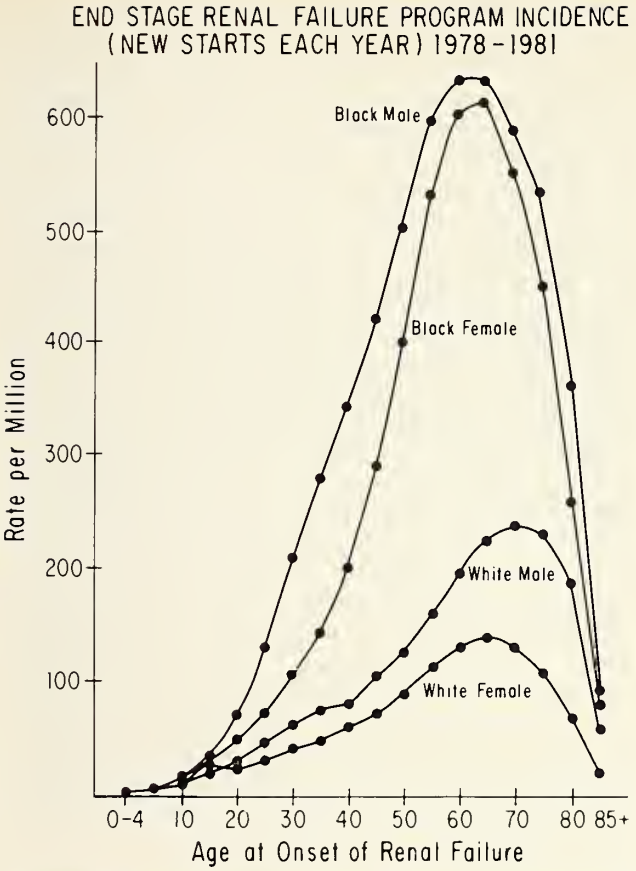


Figure 1. *ESRD Program incidence (number of new starts per year per million population of same age, sex and race) displayed by demographic status. Data are from the HCFA Medical Information System.*

approaching 500 persons on maintenance dialysis programs for every million in the population.

While it is true that each patient on dialysis does increase a facility's revenue, the principal reason for the widened admission policy nationwide was not profit, as some have claimed. It was the normal human reluctance to stand by while death overtook a person with a "treatable" disease. Each nephrologist can remember a patient everyone said was too sick to benefit from dialysis treatment but who has nevertheless surprised us by returning to a near-normal life while on maintenance dialysis. The owner-operator and academically-directed facilities of North Carolina were not immune to the desire to prolong life. Their conservative streak, however, fostered by tradition, network participation, and the tension of having to deal with severe morbidity, led to a somewhat more balanced approach to the decisions regarding patient admission. Recognizing that dialysis may only prolong dying, one physician said, "Not all terminally ill patients with renal failure have to do their dying on maintenance dialysis." Other physicians commented that they spent more time explaining the rigors and the disappointments of dialysis to very sick patients and their families than they might have spent had they admitted them to their dialysis program.

Table 1
Characteristics of Patients on Maintenance Hemodialysis Treatment Before and After the ESRD Legislation of 1972 (Adapted from Evans et al.[1])

Year	1967	1978
Estimated ESRD population	850	46,568*
Percent male	75	49
Percent white	91	64
Percent over age 54	9	48
Percent disabled	13	54

* Number enrolled under all federal programs (Health Care Financing Review, Vol. 4, page 91, 1983). As of December 1982, the combined networks reported that 67,763 Americans were on dialysis treatment.

This conservatism seems to find less expression in statistics in the country overall. In 1981 Evans et al compared the characteristics of dialysis patients before and after funding for end-stage renal disease became law (table 1).[1] These expanded admission criteria were the primary cause for the unanticipated cost increase of the program. The original intent of the law was to provide funds for those who could benefit from, but could not afford the cost of, treatment. Once enacted, dialysis and transplantation became a universal right for all patients with renal failure irrespective of their associated illness. Even with the inclusion of these unusually sick people, the per capita cost of the treatments rose slower than the general inflation rate (table 2). But the

Table 2
Change of Per Capita Cost* for ESRD Treatment as Compared with General Inflation Rate

Year	Cost Per Patient Per Year (Dollars)	Percent Change %	General Inflation Rate %	Inflation Corrected Change %
1973	13,740	—	—	—
1974	14,880	8.3	8.8	− 0.4
1975	16,472	10.7	9.3	+ 1.3
1976	17,395	5.6	5.2	+ 0.4
1977	18,679	7.4	5.8	+ 1.5
1978	18,918	1.3	7.4	− 5.7
1979	18,759	−0.8	8.6	− 7.2
Average Change		5.4	7.5	− 1.7
Total 6 Year Change		36.5	63.4	−16.5

* "Costs" are payments by the Health Care Financing Administration (HCFA) for all entitled patients' dialysis, transplantation, and hospitalization. The payments are not necessarily for an entire year of service as not all the patients are on the program for an entire calendar year. Nor do costs equal charges or costs to the facilities. In general, "costs" are 80% of "allowable" charge. However trends are considered useful data. Table is calculated from HCFA data and from the 1982 Economic Report of the President.

burgeoning number of enrollees more than overcame the reduced individual cost and the program cost soared.

Government Attempts to Control Costs

In an early effort to control costs, the Health Care Financing Agency recommended to Congress the enactment of a series of cost-control efforts. One of the first attempts was to undertake a social experiment limited to a few selected areas of the country, North Carolina included. This experiment, the Paid Aide Study, was intended to discover if offering small payment to families or friends in order to encourage patients to undertake the presumably less expensive home dialysis would save the country money by reducing the size of dialysis facilities. The experiment failed. The money for paid aides neither increased the frequency of the use of home dialysis nor reduced the cost of the program; in fact, the cost probably increased. Another effort from the Health Care Financing Agency was the requirement that local networks set numerical "goals" to increase the frequency of home dialysis usage and transplantation. Each network set its goal slightly above that which it was already achieving — a perfunctory exercise. In North Carolina we already had a relatively high frequency of home dialysis, so our goal was appreciably higher than that of most other areas.

The futility of these inducements and goals led Congress in 1982 to enact a fiscal policy reminiscent of Diagnostic Related Groups (DRG)-styled control of Medicare hospital costs. Now dialysis units are paid the same amount of money for all patients regardless of whether they are being treated by hemodialysis or peritoneal dialysis; and whether at home or in the Center (the amount is less than they previously received for just the in-Center hemodialysis treatments). This "composite rate" is intended to shift enthusiasm toward the allegedly less expensive modes of therapy, for example home dialysis. This policy is not without appreciable unintended risks. Facility costs also could be reduced by hiring fewer people or making do with less expensive equipment and supplies. Costs may also be reduced by refusal of very marginal, high-cost patients who have other serious diseases. With these concerns in mind, some members in the federal government are now re-emphasizing the networks as possible monitors of the "quality of care" of patients — a task the network, a facility-dominated organization, has always felt some discomfort with.

Data Problems

And what about the patients? How are they doing? Congress mandated a "Medical Information System" when the entitlement law was passed. The Medical Information System promised to continue the very good volunteer national registry that until then had been the responsibility of the Research Triangle Institute here in North Carolina. But the federal government's registry failed to maintain any useful assessment of patient outcome. More recently, the Medical Information System has been able to provide Congress with some assessment of the number of patients and the cost of dialysis. Even for this information, it has depended heavily on network participation. This unfortunate state of affairs has been the subject of critical editorials in prominent medical journals. For example, the *New England Journal of Medicine* asked in an editorial:[2] "Where are the data?" and reflected with despair on the fact that the European registries, despite multinational boundaries and polylingual barriers, were able to operate effectively to give their end-stage renal disease community a reasonably accurate assessment of the outcome of various groups of patients.

On its own, and despite initial opposition from the Health Care Financing Agency, the North Carolina network has begun to classify its end-stage renal disease patients by co-morbid status, as well as by age, sex, and race, and to track them prospectively. Within a year, our area may be able to begin to answer the question: "How are the patients doing?" But federal threats to cease funding the networks may undermine this effort and leave us with an expensive end-stage renal disease program costing well over 2.5 billion dollars per year — a cost that is likely to grow to twice this size — for which the government is scarcely able to give an account of the outcome of the patients the program serves.

On the brighter side, there are indications that many patients are doing well. In our own survey, we learned that two-thirds of working-age men previously employed who had had at least one year of college education, were working full- or part-time.[3] And of course no one can measure the social value of extending the lives of grandparents or family members several years past the expected date of death from uremia, even if gainful employment has not been achieved.

Research Funding — A Useful Spin-Off

Moreover, the end-stage renal disease program has maintained general awareness of the importance of treating patients with renal insufficiency before they reach "end-stage." This awareness has been translated to making research funds available and is beginning to pay off. Recent work points toward the possibility of slowing the rate of progression of renal insufficiency.[4] The important insights gained through this research include the need to control blood pressure, to reduce the work of the kidney by dietary adjustment, and to control secondary hyperparathyroidism. Arguably, most of our improvements in approach to patient care owe their development to the research stimulated by the existence of this program.

What Have We Learned?

There are lessons to be learned from this experience. One of them certainly is that once a half-way technologic breakthrough occurs in medical management, it will probably find its way into our repertoire of choices and has a very good chance of being funded. The political process and climate will determine this funding. Once funding occurs, the program is likely to change, especially with regard to the patient inclusion criteria. These events will give rise to a bureaucracy that struggles to contain costs without mandating strict admission criteria. Such a bureaucracy is likely to feel pressure to make frequent policy changes and is doomed to become quite cumbersome. The new money will also give rise to a new industry, new bases of wealth and, thankfully, some new knowledge.

Rising expectations will be the dominant feature of a

funded program. In part, these expectations are patient-specific and will lead to the inclusion of marginally (from a medical point of view) acceptable patients. In part, these expectations will be met.

The end-stage renal disease program has been neither all bad nor all good. The principal features of new programs will probably evolve along similar pathways. In the next decade, we will very likely see funding provided for the care of patients with other diseases. If Congress accepts the advice of some of the enthusiastic surgeons who are currently doing very well with the care of selected patients in their relatively small programs, funds will be provided for patients with liver failure. The initial intent will be to offer this treatment to children with absent main biliary ducts but the regulations will appear to allow inclusion of people with other diseases (possible including cancer and alcohol-induced cirrhosis) and older people. New questions will arise: Will the patients receive government funding while awaiting a cadaver graft? Will a patient whose graft fails continue to receive government funding until a new graft becomes available? When is a patient certified to be on the "waiting list" if the inclusion on that list makes him eligible for funding? Once again the government may try unsuccessfully to control total program costs without acknowledging that enrollment size is the real culprit — not individual cost. We can anticipate that national data on patient outcome will be poor unless a private volunteer system arises very quickly. The experience will again be neither all good nor all bad, but our reading of the history of the origins and practice of the end-stage renal disease program ought to allow us to anticipate some of the policy problems that are likely to be encountered.

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Lyme Disease in North Carolina

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LYME disease, originally named for an endemic area in Connecticut, is a tick-borne spirochetal illness characterized by a distinctive skin lesion, erythema chronicum migrans, by arthritis, and less commonly by neurologic and cardiac abnormalities.[1, 2] Thus far, more than 500 cases have been described, primarily in southeastern Connecticut, New York, Massachusetts, Rhode Island, Wisconsin, Minnesota, Oregon and California.[3] Recently, two patients from North Carolina with the classic skin rash of erythema chronicum migrans have been described.[4]

The purpose of the present report is to describe two atypical but serologically proven cases of the disease originating in North Carolina. The first patient, a 42-year-old woman with long-standing ankylosing spondylitis, presented with constitutional symptoms; the second, a child, was originally thought to have juvenile rheumatoid arthritis.

Now that the clinical spectrum of Lyme disease is more fully defined, a diagnostic serologic marker is available, and appropriate therapy has been documented to attenuate the primary disease and prevent secondary and tertiary manifestations, physicians and patients in North Carolina must have a high index of suspicion in order to appropriately identify and treat patients with this disorder. We predict that Lyme disease, like Rocky Mountain Spotted Fever, may in fact be common in North Carolina, but has often gone unrecognized.

Case 1

A 42-year-old research analyst with an 18-year history of HLA B27 positive ankylosing spondylitis remained well on indomethacin 75 mg daily until May of 1983 when she developed a right pretibial red papule which expanded to about 15 cm and then resolved spontaneously over about 7 days. Shortly thereafter she developed low grade fever, sore throat, headache, malaise, fatigue and anorexia and began to lose weight. She did not recall contact with a tick, although she worked daily in her vegetable garden; she had not traveled outside North Carolina in the preceding year. Symptoms persisted and she first sought evaluation in June 1983.

Examination revealed only a slight fever of 37.6°C, a 4.5 kg weight loss, mild pharyngeal erythema, and a 0.5 cm freely movable, nontender right posterior cervical lymph node. Complete blood count, urinalysis, 17 chemistry panel, throat culture and chest x-ray were normal. She was empirically treated with tetracycline 1.0 g per day for 7 days. Through July and August low grade fever, malaise, fatigue, headache and anorexia persisted and total weight loss reached 19 kg. Physical examination remained otherwise negative, without physical stigmata of reactivation of the spondyarthropathy. Abdominal ultrasound was normal as was a lumbar puncture. Spinal fluid revealed only 2 lymphocytes/mm^3 and was negative for bacterial, fungal, mycobacterial, and viral organisms. Negative serologic studies included antistreptolysin O; *Salmonella* O antigens A, B, C and D and H antigens A, B, C, D; Leptospirosis; Toxoplasmosis; Rubella; Rubeola complement fixation and hemagglutination inhibition; Monospot; *Mycoplasma* complement fixation; Cytomegalovirus; Herpes simplex virus; Respiratory syncytial virus; Eastern Equine Encephalitis; Western Equine Encephalitis; Saint Louis Encephalitis; Cryptococcal antigen; Rickettsial agglutinins for *Proteus* OX2 and OX19 and FTA Abs. The indirect immunofluorescence test for *Ixodes dammini* spirochete was positive at a titer of 1:256 on 8/11/83 and at a titer of 1:512 one month later.

When the serologic study for Lyme disease returned positive in a diagnostic range ($\geq$1:128), she was again treated with tetracycline 2.0 g/day for 20 days. Two days after the institution of this therapy she experienced a Jarisch-Herxheimer-like reaction with low grade fever, myalgia and chills. Tetracycline was continued and all symptoms subsequently subsided.

Case 2

A 5½-year-old white boy was well until April 1983 when expanding erythematous macules appeared on the dorsal aspect of both wrists and enlarged to 5 cm. These resolved spontaneously in three weeks. In May 1983 he was hospitalized with fever, exudative tonsillitis, and an acral petechial rash. His parents had removed multiple ticks from him daily over the preceding two months.

There was no adenopathy or organomegaly. The white blood count was 22,000/mm^3 with 60 percent lymphocytes (many atypical). Liver function tests were normal. OX-19 and monospot serologies were both reported as "positive." He was treated with intravenous penicillin and tetracycline and his rash and white blood cell count improved.

He returned to his private pediatrician in June 1983 with a chronic diffuse papular rash, recurrence of fatigue, and swollen tender ankles and elbows. He was rehospitalized to rule out rheumatic fever. His temperature was 38°C, pulse 96, respirations 24 and blood pressure 114/80. He had minimal cervical adenopathy, a benign systolic murmur at the left lower sternal border, and a barely palpable spleen. The hemoglobin was 12.1 g/dl and the white blood cell

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count was 9,400 with 57 polymorphonuclear leukocytes, 1 band, 39 lymphocytes, 1 monocyte, and 2 basophils per 100 cells. The Westergren sedimentation rate was 40 mm/hr. Twelve chemistry panel was normal, as were the electrocardiogram and chest x-ray. The *Proteus* OX-2 agglutinins were positive at 1:160. The ASO titer was 12 Todd units. The VDRL and rheumatoid factor were negative. He was discharged on 1800 mg of aspirin daily. Soon after, he developed arthritis of the right wrist and was referred to North Carolina Memorial Hospital for rheumatology consultation with a provisional diagnosis of juvenile rheumatoid arthritis.

His history was otherwise totally negative for abnormalities of skin or hair, mucosa, eyes, cardiorespiratory, gastrointestinal, genitourinary or neurologic systems and was negative for symptoms in other joints or the back. At the time of consultation, all joint symptoms had resolved and the physical examination was entirely normal. Slit lamp examination was negative for uveitis. The hemoglobin was 12.2 g/dl, white blood cell count 7,200 with a normal differential. Urinalysis, Westergren sedimentation rate, rheumatoid factor and antinuclear antibody were all normal. Indirect immunofluorescence test for *Ixodes dammini* spirochete was positive at a titer of 1:128 (IgG). There has been no recurrence of symptoms.

Discussion and Review of Lyme Disease

North Carolina has the highest incidence (22 percent) of cases of Rocky Mountain Spotted Fever occurring annually in the United States.[5] The present report documents the presence of Lyme disease, another tick-borne disease, in North Carolina. The prevalence of the disease is unknown, but it may well be high and unappreciated. In order to establish the diagnosis of Lyme disease, physicians, other health professionals, and patients must appreciate the variable manifestations of this disorder, have a high index of suspicion, seek serologic confirmation when indicated, and initiate appropriate therapy in order to avoid the chronic manifestations of the disease. The late manifestations may not respond well to appropriate antibiotic therapy begun later in the course. The disorder has been well described in a series of papers which we will briefly summarize.

Both of our cases illustrate some features of the difficulty in differential diagnosis. In neither case were the skin lesions classic for erythema chronicum migrans. Case 1 did not seek medical attention when the skin lesion was present and gave no history of tick bite. Case 2 was initially thought to have Rocky Mountain Spotted Fever, possibly infectious mononucleosis, then acute rheumatic fever, and with the development of recurrent arthritis was thought to have juvenile rheumatoid arthritis.

Approximately 70 percent of patients do not recall a tick bite,[6] and some may develop Lyme disease without the initial characteristic skin lesion making diagnosis more difficult. Ross and Benach have recently reported a group of "pauciarticular JRA" patients without a history of erythema chronicum migrans who have serologically defined Lyme disease.[7]

Lyme disease was first described in 1975 when several mothers in Lyme, Connecticut questioned the frequent diagnosis of juvenile rheumatoid arthritis in their community.[8] The geographic distribution of the disease in New England, the upper Midwest, and on the West Coast, and the seasonal distribution of cases in March through October, with eighty percent of cases occurring in July and August, both suggested an arthropod vector-borne disease. Subsequently a small tick, *Ixodes* species, which feeds on deer and other mammals and rodents, was implicated.[3] In the Northeast and Midwest, *Ixodes dammini* has been implicated, on the Pacific Coast *Ixodes pacificus,* and a closely related tick, *Ixodes scapularis,* may be implicated in the South. The tick is small, and the disease may also be carried by the nymph, which is 1 mm long, which would explain the lack of identification by patients.

The pathogen has recently been identified as a new spirochete, thus far designated only as the *Ixodes dammini* spirochete, which has been isolated from 5 of 96 patients, three of the isolates from blood, one from cerebrospinal fluid, and one from the margin of a skin lesion.[2, 9] With present techniques, the spirochete is difficult to culture and is isolated only on modified Kelly's medium. The spirochete resides in the mid-gut of the tick, and presumably gains entry to man at the site of the bite, which becomes the central papule of erythema chronicum migrans. The percentage of ticks infected varies with the endemic area, with 26 percent of ticks infected in the Lyme area[2] and 61 percent of ticks infected in the Shelter Island game reserve in New York.[10]

The spirochete stains with Giemsa stain and on dark field examination "moves sluggishly and rotates slowly."[10] On electron microscopy it bears some similarity to *Borrelia;* the spirochete is irregularly coiled, 10-30 μm long and 0.18-0.25 μm in diameter. Near each tapered end, 4-8 filaments originate in a line along the longitudinal axis.[10] When infected ticks were allowed to feed on rabbits, the rabbits developed skin lesions similar to erythema chronicum migrans 10-12 weeks later which lasted for about eight weeks.[10] All rabbits developed antibodies to the spirochete in titers equal to or greater than 1:1280. Serum samples from patients have been shown to have antibodies to the *Ixodes dammini* spirochete.[2, 10] IgM antibodies peak at 3-6 weeks in patients with erythema chronicum migrans, in titers equal to or greater than 1:128 in 90 percent of patients and in only three of 80 normal subjects. In 95 patients with late manifestations after several months, 94 percent had IgG titers of 1:128 or greater, while none of 80 normal subjects did.[2] Thus, the tick-borne *Ixodes dammini* spirochete is the causative agent of Lyme disease. Both of our patients were atypical, but met the necessary clinical and serologic criteria for diagnosis.

Stage I disease begins 3-32 days (median 7 days) after the tick bite especially on the thigh, groin, or axilla. Erythema chronicum migrans characteristically begins as a central papule and gradually expands to a median diameter of 15 cm (range 3-68 cm) with a bright red outer border, usually flat, hot and with a burning sensation, with central clearing. The center area may also become vesicular or necrotic, turn blue, or manifest concentric rings.[5] Other skin lesions include multiple annular secondary lesions, malar rash, conjunctivitis and diffuse urticaria with vasculitis. Median duration is 28 days untreated (range 1 day to 14 months), but only 5-9 days with antibiotic therapy. Secondary le-

sions occur only in untreated patients. They are generally smaller, migrate less and do not have induration in the centers. They may be located anywhere except the palms and soles.

Malaise and fatigue are the most common symptoms that accompany erythema chronicum migrans. Lethargy, headache, fever, chills, stiff neck, arthralgias, myalgias and lymphadenopathy are also frequently observed. These early symptoms and signs are typically intermittent and variable during a period of weeks except for the constant fatigue and lethargy.[6] These early manifestations are easily confused with viral infections, especially when erythema chronicum migrans is absent or missed. In Lyme disease the most characteristic feature of all the otherwise nonspecific symptoms is their intermittent and rapidly changing nature.

Weeks to months following erythema chronicum migrans Stage II disease may occur, with cardiac and neurologic abnormalities. Arthritis is characteristic of Stage III disease, and is seen particularly in patients who are tissue type HLA-DRw2.[11] Carditis has been reported in approximately 8 percent of patients with Lyme disease, usually about three weeks after onset, and lasting three days to six weeks.[12] The most common findings are varying degrees of atrioventricular block including first degree, Wenckebach, and complete heart block, which may present with syncope and require a temporary pacemaker. Diffuse myopericarditis and decreased left ventricular function are also known to occur. True valvular disease is not reported. Heart involvement is frequently seen concomitantly with neurologic abnormalities and arthritis.

Common laboratory abnormalities in these patients are elevated Westergren sedimentation rate, IgM, and cryoglobulins containing IgM. Neurological manifestations have been reported in 11 percent of patients with Lyme disease.[13] The most common pattern is a fluctuating aseptic meningitis with superimposed cranial and peripheral radiculoneuropathy, although encephalitis, chorea, cerebellar ataxia, mononeuritis multiplex, and myelitis have been seen.[13] Unilateral or bilateral Bell's palsy may occur. Abnormalities appear while erythema chronicum migrans is still present or 1-6 weeks after it has disappeared. During attacks patients have cryoglobulins present in serum and circulating immune complexes as detected by the binding assay for the Clq component of complement.[14] These assays improve or become negative during remission. High dose intravenous penicillin has recently been shown to shorten the duration of meningoencephalitic symptoms in patients with Lyme disease; motor deficits usually require a mean of 7-8 weeks for complete recovery despite antibiotic therapy.[15]

Lyme arthritis occurs in about 50 percent of untreated patients from weeks to years after erythema chronicum migrans develops. Most patients have the sudden onset of a recurrent, asymmetric oligoarthritis of large joints, particularly the knees. The initial episode may be brief and migratory. Typically the knees are swollen and warm, but not red. The major functional impairment is difficulty in ambulation. Synovial fluid white cell counts are usually inflammatory but widely variable with 2,000-72,000 cells/mm^3 and about 80% polymorphonuclear leukocytes.

Lyme arthritis is often confused with pauciarticular juvenile rheumatoid arthritis (as in our Case 2) except when there is a history of erythema chronicum migrans.[8] It is important to pursue this history over a period of weeks or even years. Ten percent of patients with Lyme arthritis go on to develop chronic arthritis, usually of the knees, with synovial thickening, pannus formation, and popliteal cysts in a pattern indistinguishable clinically or pathologically from rheumatoid arthritis.[11] Morning stiffness, rheumatoid factor, ANA and subcutaneous nodules are usually absent. Tissue typing often reveals HLA-DRw2, whereas HLA-DRw4 is characteristic of adult rheumatoid arthritis and HLA-B27 of spondyarthropathies.

Early in the course of the disease an elevated Westergren ESR is the most common laboratory abnormality. Only 10 percent of patients exhibit anemia or leukocytosis with a left shift. Mild abnormalities of liver function tests may be seen. Elevated total serum IgM is seen in 33 percent of patients.[1] Circulating immune complexes may be present with ECM, and persistently high levels are more commonly seen in patients who develop carditis or chronic arthritis.[12, 14] Positive cultures for the *Ixodes dammini* spirochete require special medium (modified Kelly's) and the yield is low. Indirect fluorescent antibody titers against the *Ixodes dammini* spirochete have been helpful in difficult diagnostic cases but are available only through the Communicable Disease Center in Atlanta, the State University of New York at Stony Brook (N.Y. Health Department), or through individual research laboratories. [Serum specimens may be mailed to the Division of Rheumatology and Immunology, 932 FLOB Bldg. 231H, University of North Carolina, Chapel Hill 27514.] IgM antibody titers rise initially and reach a peak between the third and sixth week after the onset of the disease. Titers of IgG antibodies rise more slowly and are sensitive and specific during later stages of the disease at titers of 1:128 or greater.[2]

Treatment

Treatment of early Lyme disease with antibiotics has improved the morbidity, especially by preventing the major late complications of carditis, neurologic sequelae and arthritis. Antibiotics also shorten the duration of erythema chronicum migrans and the constitutional symptoms. Recent studies have shown tetracycline to be the drug of choice, followed by phenoxymethyl penicillin and erythromycin.[16] Specific recommendations at this time in adults are: 1) tetracycline 250 mg p.o. q.i.d. for at least 10 days and as many as 20 days if symptoms recur or persist; 2) in the pregnant female phenoxymethyl penicillin 500 mg q.i.d. for the same duration; 3) erythromycin 250 mg q.i.d. in patients allergic to penicillin. Tetracycline should be avoided in children less than nine years of age because of dental staining; phenoxymethyl penicillin 50 mg/kg/day in divided doses for the same duration, or in the case of penicillin allergy, erythromycin 30 mg/kg/day in divided doses for 15 or 20 days, is recommended. All three drugs have been shown to prevent recurrent erythema chronicum migrans, but occasionally stage II and stage III disease have been seen with phenoxymethyl penicillin and erythromycin, but not with tetracycline.[16] For adults with Lyme meningitis, penicillin G, 20 million units/day in divided

doses for 10 days is recommended, or tetracycline 500 mg q.i.d. p.o. for 30 days in the penicillin-allergic patient.[15]

Treatment of the conduction abnormalities of Lyme carditis depends on their severity. Patients with first degree heart block can be carefully followed as outpatients, but those with higher degrees of block should be hospitalized. Patients with complete heart block should have a temporary pacemaker. Prednisone has been used in some patients with carditis in uncontrolled studies. Aspirin or other nonsteroidal antiinflammatory drug is the treatment of choice for chronic arthritis. Intraarticular steroids may be helpful in selected cases, and occasionally synovectomy has been performed in patients with progressive erosive disease.[11]

Now that the disease has been recognized in North Carolina, an effort at education of health professionals and the public is justified. In addition, surveys of ticks for incidence of spirochetal infection to assess infective risk, and a high index of clinical suspicion are needed in order to identify and treat this fascinating new multisystem disorder caused by the tick-borne *Ixodes dammini* spirochete.

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Percutaneous Fine Needle Aspiration Biopsy of the Lung: East Carolina University School of Medicine/Pitt County Memorial Hospital, 1983

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ALTHOUGH the percutaneous approach to diagnosing pulmonary disease was first performed in the 19th century, it was not until the recent development of fine needle techniques that it became a popular diagnostic procedure. Much of its recent acceptance and success can be attributed not only to the development and use of these fine, small-bore needles (20-23 gauge) but also to the application of improved radiologic techniques. These include image intensification, fluoroscopy, and the more recent dramatic development of imaging techniques such as computed tomography (CT). Improved cytologic methods, together with decreasing incidence and severity of complications, have added further impetus to the procedure.[1]

Multiple reports have attested to the safety and diagnostic accuracy of the procedure for evaluating pulmonary masses and complex intrathoracic diseases.[2-4] Approximately 450 fine needle aspirations of the lung have been performed at East Carolina University School of Medicine/Pitt County Memorial Hospital over the past five years. The purpose of this paper is to report our experience during the year 1983 and to encourage the use of percutaneous fine needle aspiration biopsy of the lung as a diagnostic procedure.

Materials and Methods

The procedure is similar to methods previously described.[1, 3] Prior to the study, informed consent is obtained following discussion of the possible complications of the procedure, including pneumothorax and/or bleeding. Mild sedation is usually given. Old and recent films are reviewed with special attention to the chronicity of the lesion, the presence of calcium, and the presence of mass or infiltrate. Identification of multiple lesions, mediastinal lesions, mediastinal or hilar adenopathy, and the true depth of the lesion are often best estimated by means of CT. From these various studies, the most direct vertical approach to the lesion is considered.

The puncture technique consists of positioning the patient so that the lesion closest to the chest wall is facing upward.[2] The effect of respiration on tumor movement can be seen by fluoroscopic examination. The depth needed for the needle's penetration is estimated and this measurement is transferred to the biopsy needle at which point the needle is clasped with a rubber-tipped forceps. A cradle x-ray table top or biplane fluoroscopy facilitates accurate needle placement. The skin surface is cleansed with Betadine, local anesthesia is injected into the skin, followed by a small skin stab wound. A 22-gauge (0.6 mm) biopsy needle, held by the rubber forceps at the estimated depth, is then guided into the lesion in a direction parallel to the x-ray beam. It is positioned so that the needle tip and hub are superimposed on each other and on the target. Occasionally, the needle must be angled to avoid skeletal interference. If possible, a puncture is performed above the rib in order to avoid the intercostal artery. There is less chance of pneumothorax if both pleural surfaces are penetrated with one motion and the fissures are not crossed. Often a "gritty" feel is transposed to the needle tip when a tumor or lesion is entered. One can prove accurate placement if the needle tip stays with the tumor on rotation of the cradle top, or if the nodule moves when the needle hub is moved. Sometimes a lateral projection film is necessary to document the needle tip position. When the needle point has been placed in the desired position, the stylet is removed, a 20 ml syringe is attached, and the needle is moved to and fro. Suction is then applied, with further to and fro motion, with the tip within the lesion. The vacuum is released before the removal of the needle, and both the needle and syringe are withdrawn. The syringe is then detached from the needle, filled with air, and reattached, and the needle contents are expressed onto the center of a sterile frosted end-glass slide. An assistant usually helps prepare the slides.

The smear technique consists of compressing the material on the slide with another slide and spreading this material over a small area similar to the preparation used in bone marrow aspirate. The majority of the smears are immediately wet-fixed in 95% alcohol while a few others are air-dried. One or more of the air-dried smears are immediately delivered to the pathologist who performs a rapid modified Wright stain (Diff-Quik).* The staining process takes approximately 20 seconds and the slides are examined wet. The pathologist will then decide on the adequacy of the sample and whether an additional procedure needs to be performed. The pathologist usually gives

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* Available from Harleco, a Division of American Hospital Supply Corp., 480 Democrat Road, Gibbstown, NJ 08027.

Table 1
Indications

Suspected malignancy:

- other non-operative techniques unsuccessful
- thoracotomy undesirable; patient refuses surgery
- multiple pulmonary lesions
- known primary elsewhere
- non-vascular hilar or mediastinal masses
- pre-op small peripheral nodule

Complicated pulmonary lesions:

- immunosuppressed patients
- complex pneumonias
- abscess; pseudotumor
- diffuse pulmonary disease (?)

Capture viable tumor cells for culture and chemosensitivity testing

his preliminary diagnosis in person in the radiology department procedure room where he can review the x-rays and directly confer with the radiologist. The immediate "quick-read" procedure can usually be performed within five minutes. At this time, any additional material can be allocated for further studies including microbiologic examination, cell block and electron microscopy. The remaining 95% alcohol fixed slides are examined within one or two hours and the final diagnosis is rendered. The pathologist contacts both the radiologist and the patient's physician.

Following the biopsy procedure, the patient is checked for immediate and/or delayed pneumothorax and parenchymal or pleural hemothorax. Vital signs are recorded and the patient is observed for hemoptysis.

Indications and Contraindications

Indications for fine needle aspiration biopsy at PCMH are outlined in table 1. The main indication is obtaining a definite diagnosis of a persisting localized lesion of the lung. The contraindications are presented in table 2.

Results

Seventy-four patients underwent 84 biopsies at Pitt County Memorial Hospital in 1983. The age range was 37 to 83 years old with 42 males and 32 females.

Table 2
Relative Contraindications to Percutaneous Needle Aspiration of the Lung

- uncooperative patient
- severe recent hemoptysis
- bleeding diathesis
- severe pulmonary hypertension
- aneurysm, pulmonary arteriovenous malformation, pulmonary varix
- COPD (PO_2 < 60 mm Hg; < 50% predicted airflow)
- large bullae
- only one functioning lung
- hydatid cyst

Table 3
Cytologic Diagnosis

Diagnosis	Number
Squamous cell	16
Adenocarcinoma (including alveolar cell)	16
Large cell undifferentiated (including giant cell)	5
Small cell carcinoma	4
Poorly differentiated	5
Metastatic malignant schwannoma	1
Atypical (compatible with malignancy)	5

Forty-seven definite malignant diagnoses were rendered along with five highly atypical diagnoses. For discussion purposes, both groups are combined to represent 52 positive diagnoses. There were 32 negative cases. Four of the negative cases were later shown to be malignant by histologic examination for a false negative rate of 7.1%. There were no false positives. The sensitivity of the procedure (true positive) was 93% and specificity (true negative) was 100%.

The types of malignancies diagnosed in the 52 positive aspirations are presented in table 3. As noted, 47 relatively specific diagnoses were given with only five patients having a non-specific atypical diagnosis. Of the 16 patients having a histologic examination of their lung lesions, only three patients had discordance of diagnosis for a cytologic/histologic correlation rate of 81.3% (table 4). A number of

Table 4
Correlation Between Cytologic and Histologic Classification

	Histology					
Cytology	Squamous Cell	Adeno.	Large Cell	Small Cell	Poorly Diff.	Other
Squamous cell	3	1				
Adeno		3				
Large Cell				1*		
Small Cell				1†		
Poorly Diff.	1				1	
Atypical	1	3				
Other						1

* Small cell carcinoma diagnosed initially by bronchial biopsy and aspiration performed the next year to evaluate recurrence.
† Undifferentiated malignancy diagnosed initially by histologic examination with aspiration cytology performed to give more specific diagnosis. Aspiration cytology and electron microscopy of aspirated material gave specific diagnosis of small cell undifferentiated carcinoma (oat cell carcinoma).

Table 5
Complications of 84 Biopsies

Pneumothorax — Total	— 27%
Minor (no tube)	— 17%
Requiring tube	— 10%
Hemoptysis	— 3%
Minor parenchymal bleed	— 2%

the 32 negative diagnoses were relatively specific including two granulomatous diseases (cryptococcus and atypical tuberculosis), one aspergillosis, one abscess, and one pulmonary infarct.

The complications of the procedure are all relatively minor (table 5). The pneumothorax rate was 40% earlier in the year, but declined to 21% following the uniform institution of the "quick-read" procedure with an overall percentage of 27 for the full year. The "quick-read" procedure allows for an answer regarding adequacy of the biopsy sample within several minutes, and made it possible to abandon the previous routine use of multiple punctures considered necessary to assure a diagnosis.

Discussion

The main value of pulmonary fine needle aspiration biopsy is in the diagnosis of malignancy with an accuracy rate of 80 to 95% in most recent series and exemplified by our 1983 experience.[1, 5] A definite diagnosis can be given in most patients with minimal trauma, shorter hospital stay and at lower cost. Patients who are poor surgical risks are saved a thoracotomy and others who are clinically inoperable can receive appropriate chemotherapy or radiotherapy without major surgery performed solely for diagnostic purposes.

Fine needle aspiration biopsies have been shown to be superior to bronchoscopic biopsies and sputum cytology in the diagnosis of radiologic evident lesions.[6] Sputum cytology still remains the method of choice for screening patients with early non-radiographically visualized lesions. Bronchial brush biopsy is especially valuable for evaluation of central bronchial lesions. The combined use of all three cytologic sampling procedures can insure the highest degree of accuracy in the evaluation of intrathoracic lesions.

The diagnostic yield of fine needle aspiration biopsy exceeds other methods short of surgery, since 90% of all malignancies can be accurately diagnosed with a false negative rate in most series between 7 and 10% and a false positive rate between 1 and 2%.[1, 5] The procedure works best when there is joint cytopathologic and radiologic cooperation and expertise. In recent years there has been increasing application of pulmonary fine needle aspiration throughout the U.S., not only for the diagnosis of malignancy but also in the evaluation of complex lung disease.

Our experience again re-emphasizes that fine needle aspiration biopsy of the lung is simple, accurate and usually safe and can lead to quicker, less expensive non-invasive diagnoses of benign and malignant lesions.

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Health Care Planning in North Carolina: Migrant Workers Program

Michael F. Fleming, M.D. and Charles S. Hayak, B.S.

OVER 40,000 migrant agricultural workers labor in the fields of North Carolina between May and October each year. There is "almost universal agreement that migrant farmworkers have the lowest health status of any group in the United States."[1] In seven countries where large numbers of migrants work, the prevalence of tuberculosis varies from 12.5 to 64.4 cases per 100,000. The state rate is 17.4 cases per 100,000 population.[1] The infant mortality rate for migrant farmworkers from records at Tri-County Community Health Center (TCCHC), 1982, was 30 deaths per 1,000 live births in contrast to 13.7 : 1000 for the state.* This paper presents an overview of the North Carolina migrant health care system.

Dunbar and Kravitz have described migrant farmworkers as "freelance workers who drift from farm to farm, often covering thousands of miles in a month, seeking temporary jobs during the short-lived times of plenty, the cultivating and harvesting times when the crops and the land itself must be served with no time to waste."[2] This is in contrast to seasonal farmworkers, state residents, who do agricultural work each growing season. There are three major streams where migrant workers follow the agricultural harvest: the West Coast Stream, Midcontinent Stream, and East Coast Stream[3] (figure 1).

Every spring approximately 40,000 migrant workers move into North Carolina to work the agricultural fields, cultivating and harvesting tobacco, sweet potatoes and other crops. This temporary and mobile work force supplements the state's 200,000 resident farmworkers, giving the state the largest farmworker population on the East Coast and the fourth largest in the United States.[1] Of North Carolina's one hundred counties, 25 had over 2,000 migrant and seasonal farmworkers in 1980[4] (figure 2). The migrants who work the fields in North Carolina typically are 50-60% black Americans, 25-30% Mexican Americans, and 15% either Haitians or white.[1]

In the migrant farmworker population, serious public health problems normally associated with underdeveloped areas are the rule rather than the exception. Common medical problems seen in migrant populations include tuberculosis, parasites, venereal disease, malnutrition, alcoholism, and violent injuries.*[8] The health problems of this occupational group are tightly interwoven with their culture, environment, and occupation. Poverty, overcrowding, poor housing, poor sanitation, poor education, stress of the camp and work, and chronic exposure to pesticides are daily health risks.

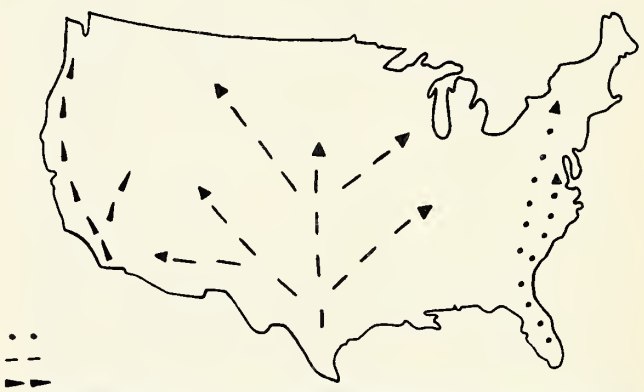


Figure 1. *Major streams of migrant travel. The East Coast (●), Midcontinent (--), and West Coast (▶) streams are the three major routes of migrant travel.*

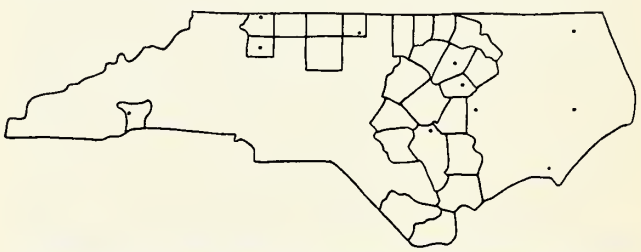


Figure 2. *Migrant health programs (●) and counties with high density migrant and seasonal farmworkers, 1980. Twenty-five of the state's 100 counties had more than 2000 migrant and seasonal farmworkers in 1980. Seven of the eleven migrant health programs surveyed are located in these counties.*

The health care system for migrant farmworkers in the state comprises county health departments, federally funded migrant clinics, local hospitals, and provider physicians. The majority of migrant workers, nationally and in this state, receive their care at county health departments and federally funded migrant health clinics.[3] Hospitals also play an important role, providing emergency treatment, inpatient care, and specialty consultation. Obstetrical de-

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* Watkins EL, Peoples MD, Gates C: Health and social needs of women farmworkers receiving maternity care at a migrant health center. Presented at the 111th Annual Meeting of the American Public Health Association, November 1983, Dallas.

* Grant application program narrative, TCCHC, Newton Grove, NC.

liveries are usually done at local hospitals. Due to economic, communication, and transportation barriers, private physicians are least utilized by migrants for initiation of care. As transient workers, migrants have difficulty qualifying for federal and state assistance programs.[3] The state's Migrant Health Program reimburses for physicians at Medicaid rates and hospitals at $125 per day both for a maximum of three days.*

In North Carolina, migrant health care in counties not served by federal programs is overseen by the Migrant Health Program (MHP) of the Department of Human Resources. The MHP receives state and federal funding for provision of care. In 1981, the Program's budget was $450,000 ($251,000 federal). As in other states along the migrant stream, North Carolina's program's funds are mainly utilized through county health departments, some of which operate special migrant programs[6] (table 1 and figure 2). Only health departments operating special migrant programs record separate data on migrant visits. As mentioned, money is also budgeted for reimbursement to hospitals and private physicians who provide care to migrants. Because of limited funds, priority is given to hospitalizations for deliveries, infants, and children.[6] The major thrust of the state's migrant health program, then, is handling of acute medical problems rather than prevention of illness. Brown has written that in the migrant health care system, "prevention as a point of view cannot coexist with the pressure of acute clinical activities."[7]

Clinics may offer three types of health care services: ambulatory care clinics for management of acute and chronic illness; preventive medicine programs which include the Supplemental Food Program for Women, Infants, and Children (WIC), family planning, and nutrition counseling; and outreach programs which send health personnel and volunteers into migrant camps where persons are screened for blood pressure, serious illness, and medication needs.

In addition to county health departments, two locally administered migrant health centers receive funding from the federal government's Public Health Service, Department of Health and Human Services, the Office of Migrant Health of the Bureau of Health Care Delivery and Assistance. These centers are the TCCHC in Newton Grove and the Migrant Family Health Service (MFHS) in Hendersonville.

The TCCHC serves Harnett, Johnston, and Sampson counties (1,962 square miles). There are over 200 migrant camps in this area, with an estimated 10,000 migrant workers (one-fourth the state's total). The Employment Security Commission estimates that there are 7,125 seasonal workers in the clinic's catchment area. This clinic is the state's only special migrant clinic that operates full-time year-round. The MFHS serves mainly Henderson, Polk, Burke, Haywood, and Rutherford counties, and migrants from northern South Carolina. This clinic operates only four months each year. As in many migrant clinics, nurse practitioners provide a majority of the care. The TCCHC utilizes two nurse practitioners and one full-time physician while the MFHS employs three nurse practitioners and one part-time physician.

Table 1
Federal and State Migrant Clinics Surveyed

Federal
Tri-County Community Health Center, Newton Grove
Migrant Family Health Service, Hendersonville
State
Albemarle North (Camden, Currituck, Pasquotank Counties)
Carteret County Health Department
Greene Health Care, Inc. (Greene County)
Hyde County Health Department
Nash County Health Department
Prospect Hill Clinic (Caswell, Alamance Counties)
Surry County Health Department
Wilson County Health Department
Yadkin County Health Department

This paper presents the results of a survey of eleven migrant health care programs in the state. These include the two federally funded migrant health care clinics discussed above and nine health departments or clinics which offer migrant health programs (table 1). The results suggest important factors and programs that should be considered when providing migrant health care.

Methods

A telephone survey of the state's two federally funded migrant clinics and nine clinics (county health departments and one private clinic) that offer special migrant programs was performed (table 1). Data collected include number of migrant outpatient encounters, number of referrals, number of migrants screened by outreach, and number of migrants served at evening clinics during 1982. In addition, the number of referrals that were inpatient hospitalizations, outpatient clinic or specialist referrals, and dental referrals was obtained.

All eleven clinics were able to provide some of the data requested. Five of the eleven clinics were able to give tabulated data. One clinic, Greene, could only provide estimates, with the remainder providing both tabulated and estimated data. Only two clinics (Greene, Prospect Hill) were unable to give tabulated data for the number of outpatient visits. The number of hospitalizations from the TCCHC records includes both referrals directly from the clinic and known hospitalizations of migrants in its catchment area. The MFHS and Greene Health Care clinic could not provide breakdown on referrals. Albemarle, Nash, and Yadkin clinics could only provide a partial breakdown. Six of nine clinics, one federal and five state, performing outreach were able to provide numbers of migrants screened. All five clinics offering evening clinics were able to report numbers served.

Results

Data on outpatient encounters, referrals, outreach, and evening clinics are summarized in table 2. There was a total of 12,003 outpatient encounters reported. The federal clinics served 9,165 or 76.3% of these encounters compared with 2,838 or 23.7% at state clinics. Nash and Carteret

* Personal communication with Ms. Dara Murphy, director Migrant Health Program, N.C. Department of Human Resources.

Table 2
Services Offered and Number of Migrants Served by Federal and State Clinics, 1982

Clinic	Outpatient Encounters #	% of total	Referrals #	% of OP	Outreach #	% of OP	Evening Clinic #	% of OP
Federal								
TCCHC	5,165	43.0	1,636	31.7	4,328	83.8	not offered	
Hendersonville	4,000	33.3	—	—	conducted		160	4.0
Subtotal	9,165	76.3	1,636	>17.9	>4,328	>47.2	160	1.7
State								
Albemarle	322	2.7	74	2.3	475	148	480	149
Carteret	0	0	0	0	not conducted		35	—
Greene Health	50	0.4	—	—	not conducted		not offered	
Hyde	180	1.5	127	70.6	200	111	95	52.8
Nash	0	0	>48	—	>3,500	—	1,011	—
Prospect Hill	950	8.0	27	2.8	1,500	158	not offered	
Surry	74	0.6	78	105	conducted		not offered	
Wilson	840	7.0	442	52.6	500	59.5	not offered	
Yadkin	422	3.5	127	30.1	conducted		not offered	
Subtotal	2,838	23.7	>923	>32.5	>6.175	>218	1,621	57.1
Total	12,003	100	>2,559	>21.3	>10,503	>87.5	1,781	14.8

County programs served migrant outpatients through evening clinics instead of during general clinic hours unless needs were emergent.

Reported referrals were 1,636 from the TCCHC federal clinic, 31.7% of its outpatient encounters, and more than 923 for state clinics, 32.5% of their outpatient encounters. The breakdown of these referrals into inpatient hospitalization, outpatient referral, and dental referrals is shown in table 3. There is a statistically significant difference between federal and state hospitalizations as a percentage of outpatient encounters ($P < 0.001$, Z test for difference of proportions). However, the TCCHC data include all known hospitalizations from its catchment area rather than hospitalizations directly from the clinic alone, thus increasing its reported hospitalizations.

There was no difference between state and federal clinics in outpatient referrals as a percentage of clinic outpatient encounters. The federal and state outpatient referral rates were 18.6% and 18.3%, respectively. The large number of dental referrals, 309 federal and >143 state, supports other data on the poor dental status of migrants.[3, 8, 9]

Five of eleven clinics offered evening clinics. Hendersonville served 160 migrants at these, only 4% of its outpatient encounters. On the other hand, the four state clinic evening clinics served more than 1,621 migrants, greater than 57% of total state outpatients. The seven state clinics conducting outreach screened over two times as many migrants than all nine served as outpatients. More than 10,453 migrants were seen by nine outreach programs. The TCCHC performed outreach to 4,328 migrants, 83.8% of its outpatient encounters.

Conclusions

Shenkin has described accessibility as one of four characteristics upon which a health care program should be evaluated.[3] Seven of eleven clinics contacted are located in counties with greater than 2,000 migrant and seasonal farmworkers in 1980. The TCCHC alone serves twenty-

Table 3
Breakdown of Referrals

Clinic	Total Referrals #	% of OP	Hospitalizations #	% of OP	Outpatient #	% of OP	Dental #	% of OP
Federal								
TCCHC	1,636	31.7	367*	7.1	962	18.6	309	6.0
State								
Albemarle	74	2.3	7	2.2	—	60	18.6	—
Hyde	127	70.6	6	3.3	99	55.0	22	12.2
Nash	>48	—	48	—	—	—	†	
Prospect Hill	27	2.8	13	1.4	14	1.5	0	0
Surry	78	105	1	1.4	71	95.9	6	8.1
Wilson	442	52.6	58	6.9	336	40.0	45	5.4
Yadkin	127	30.1	—	57	13.5	—	70	16.6
Subtotal	>923	>32.5	133	4.7	520	18.3	>143	>5.0

* Includes all known migrant hospitalizations from the TCCHC catchment area.
† Approximately 50% of outpatient encounters received a dental referral.

five percent of the state's estimated total migrant population. This theme of location of programs in areas with significant numbers of migrants is also present in the federal Migrant Health Act, which in 1975 began to provide funding for year-round migrant centers in areas with greater than 6,000 migrant and seasonal farmworkers. This was reduced to 4,000 in 1978 due to the rural, low density location of farmworkers. Further extensions of this theme are outreach programs and the suggestion of mobile clinics that travel to migrant camps.[3]

With a defined migrant service mandate, federal programs can better predict, plan, and utilize their facilities and staff to serve large numbers of migrants. For example, the MFHS is only open during the peak of the growing season. The TCCHC employs additional providers, translators, outreach, and transportation workers during the season. General health clinics, however, serve a broader population, and providing more comprehensive migrant care would be detrimental to other services. Finkelstein has written that "the more comprehensive the program, the greater the risk of underuse of some services, thus threatening the financial solvency of the highly used services."[10] This problem is faced by all clinics serving the general, low density rural population.[10]

Outreach programs were offered through nine of the eleven clinics. Personnel from several clinics attempt to visit all the migrant camps in their area. Three of four state clinics screened more migrants by outreach than they served as outpatients. This type of program is a means of screening large numbers of migrants quickly for several diseases, acute and chronic, that are common in a migrant population, including hypertension and tuberculosis. The majority of tuberculosis cases identified at TCCHC in 1982 was through outreach. While the state programs utilize outreach for follow-up visits, transportation arrangement, health education, and screening for acute medical problems, TCCHC also conducts a health questionnaire for chronic illness, review of systems, and blood pressure determinations. The screening, early diagnosis, ability to see large numbers of migrants, and accessibility make outreach a valuable program.

Evening clinics are another means of making care more accessible since they allow migrants to receive care without missing work and pay.[5, 8] Although only five of the programs offered evening clinics, over 1,781 patients were seen at these clinics. Two of the health departments served migrants solely through evening clinics. It is of note that the TCCHC added evening clinics for the 1983 season, and served approximately 870 persons.

Lastly, the results concerning referrals and referral breakdown suggest several conclusions. The lack of statistical difference between state and federal program outpatient referrals implies that the health status of migrants across the state is fairly homogeneous. It may also imply that services offered by the two types of programs are comparable, especially since the provider staff for both types is similar. However, the federal clinics possess better laboratory and x-ray facilities, and utilize more staff for outreach, translation and transportation. A more detailed investigation of the medical reasons for outpatient referrals would better compare the two types of programs.

Unfortunately, the hospitalization rates that the programs record are different, making comparison difficult. More than 14% of the state referrals were for inpatient hospitalization, 4.7% of their outpatient encounters. The variation in hospitalizations between state clinics themselves, 1.4% to 6.9% of outpatient encounters, and the larger number reported from the TCCHC catchment area point to the importance of local hospitals as a source of care and to differences in local clinic use for conditions requiring hospitalization. Again, further investigation and comparison between the two types of programs are needed.

In conclusion, the most comprehensive migrant programs offer ambulatory care, preventive medicine services, and outreach. Location of programs in migrant dense areas, evening clinics, and outreach improve accessibility of clinic services, allowing for increased care. In addition, outreach is one of the few attempts at early diagnosis and screening in a system of predominantly acute care. While federally supported migrant clinics in high density areas serve large numbers of migrants, only two of these clinics exist in North Carolina. Consequently, most migrants in the state are dependent on health departments and further outpatient referrals for health care. Additional studies to determine reasons for referrals and hospital inpatient use are needed.

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DESCRIPTION: CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration combines two antihypertensive agents CORGARD® (nadolol), a nonselective beta-adrenergic blocking agent, and NATURETIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations: 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide.

CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). **Bendroflumethiazide** — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS: Nadolol — Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of β_2 receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — Nadolol — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance; warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and G.I. disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalaemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, *Bendroflumethiazide*, and PRECAUTIONS, *General, Bendroflumethiazide*).

Drug Interactions — Nadolol — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents. **Anesthetics, general** — exaggeration of anesthetic-induced hypotension (see WARNINGS, *Nadolol, Major Surgery*). **Antidiabetic drugs (oral agents and insulin)** — hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, *Nadolol, Diabetes and Hypoglycemia*). **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect; monitor closely for evidence of hypotension and/or excessive bradycardia.

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics. **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of antidiabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or peripheral adrenergic blocking drugs** — potentiated effect. **Preanesthetic and anesthetic agents** — effects may be potentiated, adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, *General, Bendroflumethiazide*).

Carcinogenesis, Mutagenesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed.

Pregnancy — Teratogenic Effects — Nadolol — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose, no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women, therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus, these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol-Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported, intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash, pruritus, headache, dry mouth, eyes, or skin, impotence or decreased libido, facial swelling, weight gain, slurred speech, cough, nasal stuffiness, sweating, tinnitus, blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol. The following adverse reactions may also occur. **Central Nervous System** — reversible mental depression progressing to catatonia, visual disturbances; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis, ischemic colitis. **Hematologic** — agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat, laryngospasm, respiratory distress. **Miscellaneous** — reversible alopecia, Peyronie's disease, erythematous rash, arterial insufficiency.

Bendroflumethiazide — Gastrointestinal System — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersensitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed. Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, employ the following measures, as appropriate: **Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation. **Hypotension** — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a β_2-stimulating agent and/or a theophylline derivative. **Stupor or Coma** — Supportive therapy as warranted. **Gastrointestinal Effects** — Symptomatic treatment as needed. **BUN and/or Serum Electrolyte Abnormalities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval, see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

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Meet George Moore, Your New Executive Director

Patricia K. Hodgson

MEET George Moore. He's the new Executive Director of the North Carolina Medical Society, after a fast five month learning period as Associate Executive Director.

George Moore is a native North Carolinian, born in the small community of Pilot, "a state of mind which is close enough to Zebulon that they understand each other." He is a product of three of the State's major universities, having attended NC State, graduated with a degree in English from UNC, done graduate work in public administration and business administation, and started his first job at Duke.

That first job was an unusual one, particularly for someone just out of college. Soon after the Russians launched Sputnik I in the late 1950s, there was considerable concern in many circles in this country because America had not put up the first space satellite. Most people agreed that the nation's educational system was the primary culprit for our having fallen behind Russia in the sciences.

On the campus of Duke University was the Army Research Office, an administrative unit of the Chief of Research and Development of the Army. The Office placed research contracts, mostly with educational institutions throughout the country, and it was heavily involved in the mammoth catch-up effort in space exploration. Because of that work, the Army Research Office had excellent lines of communication with most major colleges and universities. It was the catalyst in the creation of a program designed to help produce the scientists, engineers and mathematicians the nation needed immediately and in years to come.

Enter George Moore, recent college graduate: "They hit on this notion that maybe what we ought to do is identify the really first rate minds among the high school kids in this state and expose them to bench scientists, give them some hands-on scientific experience, do some seminars, and show them what a career in science would be like." With the help of the Department of Public Instruction, the Academy of Science, and the major high schools in the state, about 350 youngsters were identified, invited to take part in the program, and spread out among the three universities in the Research Triangle area since there were too many for any one campus. Moore directed the program, the Junior Science and Humanities Symposium, from Duke and it was an enormous success for both the students and the faculty. The word shortly got out to other states, and the program grew. From the single pilot progam in the early 60s there eventually evolved a network of 25 regional centers at major universities across the country before Moore left. The culmination was a national symposium to which the brightest of the bright were invited. This was held at the U. S. Military Academy at West Point, cosponsored by the United Nations and Princeton University, and among the speakers were Werner Von Braun, J. Robert Oppenheimer, and Edward Teller.

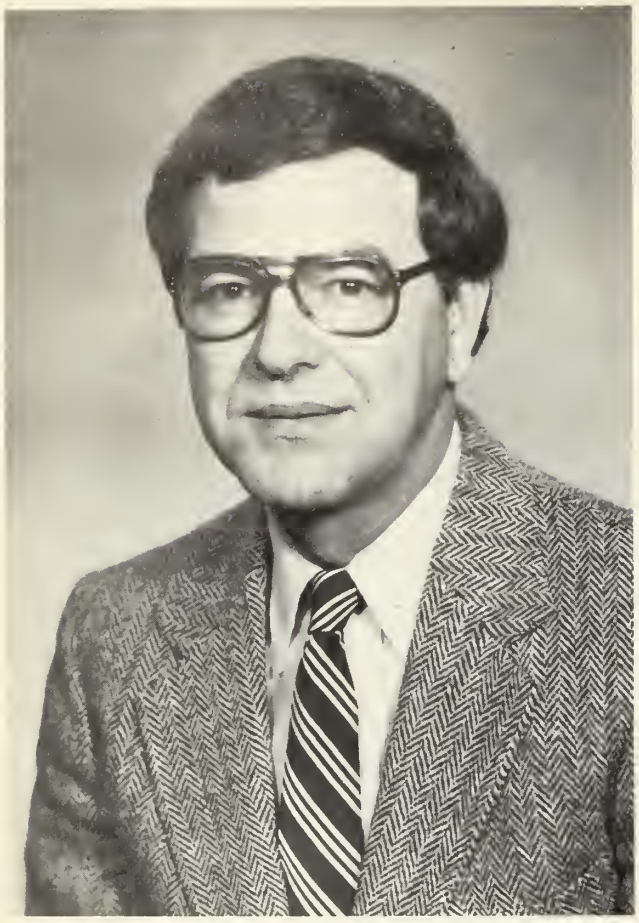
This job gave Moore exposure to almost constant travel, to the major scientific institutions, to federal agencies, to the U. S. Office of Education, to business and industry, to the generals of the Army, and to the leading scientific researchers in the country. He was lured away from that position by one of the members of the Program's Advisory Council who suggested to the Superintendent of Schools in Roanoke, Virginia that Moore might be the right person to direct the Federal progams for that school system.

Because of recent Federal mandates, there was an abundance of money available for new, innovative programs in the public schools. Moore became head of the Federal programs for the Roanoke schools: "I saw an opportunity to do some things I hadn't done at Duke. I was ready to start broadening my horizons a little bit."

The first thing they did was develop a model kindergarten program. There were no certified kindergarten teachers, the classrooms were physically inadequate for kindergarten-aged children, and there was next to no information about how to start a good kindergarten program, but they forged ahead anyway, and they succeeded. With about $500,000 in federal funds they developed certification methods, renovated school rooms, developed materials, and became the model for the state in the process.

Another interest gaining prominence at that time was the other end of the age spectrum, the undereducated adult. The Roanoke schools developed an adult basic education program during Moore's tenure there that became the model for other such programs throughout the country. A third program with which Moore was involved and of which he is very proud was the Head Start Program, which was another great success. "All in all, we had ourselves a very nice time."

Roanoke lasted about three years, and then Hollins College came calling. The reason Hollins College came calling was the Dean of Hollins, who served on the School Board in Roanoke, and came to know Moore through School



Board meetings. When Hollins found that it needed a new head of its external affairs program it came to Moore, and he went to Hollins. His responsibilities included development, alumnae relations, publications, press relations, governmental relations, and a multi-million dollar capital campaign that was just in the planning stage. "I'd never done any of this sort of thing for higher education and it seemed like one of those things that I'd like to do."

When Moore took the position at Hollins the endowment was $3 million; when he left 12 years later, it was $22 million with another $3 million in pledges. Many new facilities were constructed and many of the fine old buildings, most of which were placed in the National Register of Historic Places, were refurbished.

"The only thing that could have taken me away from Hollins was an opportunity to come back home to Raleigh. North Carolina State was looking for an Associate Vice Chancellor to do essentially what I'd been doing at Hollins. I thought about it a good while and finally decided that it was something I'd like to do."

Moore took the NC State position in 1980 and found himself facing a large and unfamiliar bureaucracy, "which took some getting used to." The fact that State is the research institution of the University system in North Carolina and the fact that State provides the trained manpower needed by North Carolina's many technology-based industries make it a particularly attractive investment for corporate philanthropy in the 1980s. Businesses invest their dollars in financial aid, in research equipment, and in faculty development in an effort to keep the finest teaching and learning minds at State teaching and learning.

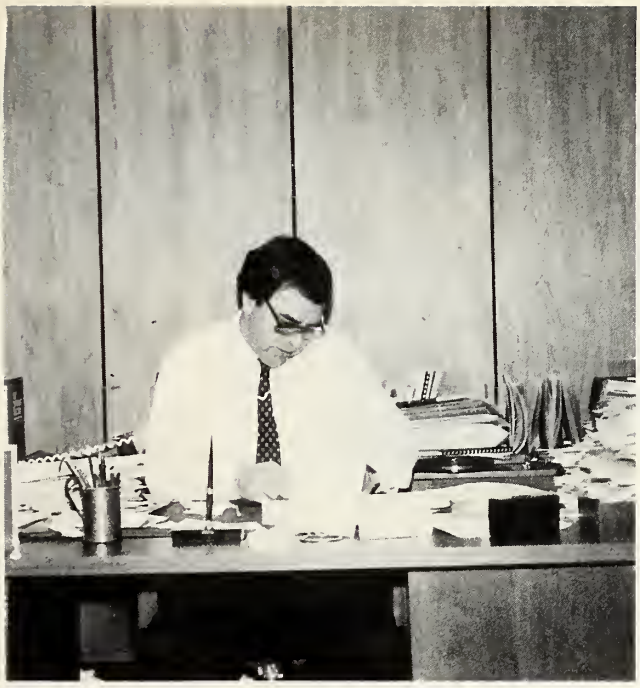
Unlike many universities, which have a centralized fund-raising structure for the entire institution, NC State has fourteen separate foundations, each chartered and incorporated and each raising funds for its own constituency. Moore's job was to coordinate the efforts of these foundations, to discover new sources of support, to guide solicitation efforts of all constituents to the most appropriate foundation, to make friends for the University throughout the state.

With a career in education from Head Start to university, what brought Moore to the North Carolina Medical Society? "Except for the medical science aspects and the issues of organized medicine, the activities and services provided to our membership are essentially the same in nature as those services provided to alumni." Many facets of NCMS organization are very similar to the services of other organizations: "administration is administration, organization is organization. I don't find the day-to-day activities of the Society in terms of working with the staff and working with the leadership very different from what I've always done."

But what *is* different? "What I do have to learn — and there is so much of it to learn — is the medical issues, the concerns of organized medicine. Those are issues that will take me a long time to be knowledgeable about. I've already learned a lot. I have a good bit of information, but information is not knowledge. Only when you can learn to use all those bits and pieces of information with some perspective does it become knowledge, and that's what I'm short of. Those issues and their implications are so much broader and deeper than I'd ever imagined them to be."

One of Moore's high priorities, which should be in place by the time you read this, is the recently created Committee on Goals and Objectives which he views as a major step forward for the Society: "I hope what will come from this is a blueprint of where we want to go over the next five year period. It will identify and address the major issues of the Society and then set out to establish some specific goals and objectives about how we handle these issues, what we should be doing, and exactly how we're going to do it. This has implications for the use of our resources, both human and financial; it will guide our budgeting process and allow us to develop realistic budget projections; and it will determine the personnel that we need and what those people will be doing in their day-to-day jobs for the Society. I really don't think we can do a workmanlike job in service to the members until we have in place that sort of blueprint."

Another high priority with Moore is membership development. "With the data provided by the recent member and non-member surveys, we have a useful source document to build on our strengths and shore up our deficiencies. We have a good notion of how we are perceived, and we can use that information to make membership in the Society more attractive. We've got to show that the product we offer is useful and worth far more than the price of membership. I hope that an intensive membership campaign is just ahead, that members will be calling on non-members to present our case and to show the importance of many voices speaking as one. We need to concentrate



especially on the younger physicians to suggest to them the importance of their role in organized medicine."

Here are some of George Moore's early thoughts on matters of concern to the North Carolina Medical Society.

- On medicine today: "Never has medicine been faced with as many serious concerns, some of which could change the way a physician practices medicine: the increasing intervention of government; the terrible concerns about escalating costs; the different ways of providing health care — the settings and the organizational systems — that are coming along that are at heart an effort to reduce the costs of health care but which may pay too little attention to the quality of care."
- On the role of businesses in the changing practice of medicine: "It's costing them an inordinate part of their resources to provide employee health care benefits. Obviously they're looking for ways to reduce their costs or at least minimize them without withholding from their employees the medical benefits that they've been entrusted to give. But these are corporate resources that will be deployed like all other resources — where they will return the greatest benefit per dollar spent: in outpatient settings, in free standing units of various sorts, with built-in financial disincentives such as co-payments, less first dollar coverage, and the like. There will be groups of physicians working together in HMOs and IPAs and Preferred Provider Organizations in ways that we couldn't even anticipate a few years ago."
- On Medicare: "The Medicare program and the government's concern about those rising costs are likely to have an impact beyond Medicare. As experience shows how well the DRGs and the peer review process will work, then I think it's only one small step from there to the adoption of these same sorts of programs by the commercial insurers."
- On the role of the North Carolina Medical Society staff: "I think the staff of the Society has to be more of a motivating force than it's ever been in the past. We've got to be seen by our membership as people who are in possession of the facts. We must have the information they need and we must see that they get that information. We've got to be more alert to opportunities to help physicians as they serve their profession through our Society, as they are wrestling with the various issues that arise. We must be mindful always that because we're hired full time to provide services, we must in many instances know more about a particular issue than the individual physician could possibly have time to know. We've got to find ways to help that physician understand the issues. We've got to anticipate needs. I want us to be a professional group that is perceived by its member physicians as just that. We have to earn that. I think too often in a membership organization the staff is reactive; they don't tend to move on matters until they get requests to do so. Clearly, policy decisions remain the prerogative of the membership, but in the day-to-day operation the staff really has to be proactive, and that is essentially what I want us to be.

"We've got here the makings of a very good staff. We must among ourselves be very proud of what we do and how we do it. I really hope that among the staff within a short time there will be the feeling that we are the very best state medical society in the country, and there's no reason why we can't be."

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The Doctor Glut

Eugene W. Linfors, M.D., editor

Dr. John Gamble of Lincolnton has encouraged us to establish a forum for communication among North Carolina doctors. This month we begin the Physicians' Forum. The members of the forum to discuss each issue will be selected by Eugene W. Linfors, M.D., who is a member of the General Medicine Division of Duke. We welcome your letters to the editor to give your opinion of both the issue of the month and the views of the doctors constituting the forum.

The question for the June issue is: **From your own experience, are we educating too many doctors? If so, what should be done and how?** *Remember, there are three primary sources of doctors: American and Canadian schools, foreign schools, and schools for American citizens established in the Caribbean. Many foreign trained doctors circumvent immigration quotas by marrying U.S. citizens.*

This new feature does not replace our regular Letters to the Editor column.

Eugene A. Stead, Jr., M.D.

From Dr. Eben Alexander, Jr., a neurosurgeon in Winston-Salem.

Demographic studies clearly point out that there will be far more physicians in 1990 per capita than there were in 1970. Physician and public surveys indicate that while physicians in general feel we have enough or possibly more physicians than we need, the public is not yet so sure of this. There are some geographical areas in which the public wants more physicians, and there are some specialties in which there are not enough physicians, but these latter are isolated and uncommon.

If the perception of a surplus is based on the situation in 1960, for example, then there is a "doctor glut." But the perception of a surplus is a relative matter, and there are a number of factors that will alter the present situation:

1) There will be 5,000,000 more persons over 65 years of age by 1990, and there will be a 75% increase in persons over 75 years of age by the year 2000. Since 1950, the number of persons older than 65 years has increased 106%, and there are more persons now alive over the age of 65 than all the persons world-wide who have lived to that age in the past.

Geriatric patients require more hospitalizations than patients younger than 65 years, and require them for longer periods of time; they also have more operative procedures. Geriatrics is a specialty that *will* need more physicians.

2) There are far more valid, effective therapeutic drugs and methods for treatment than were available 30 years ago, although many persons are still not being treated adequately with those drugs. In 1950, there were no effective drugs for hypertension; now there are scores of these drugs for various types of hypertension. When more patients need better treatment, more physicians in all fields are needed.

3) It is not likely that the physicians of the 1990s will want to work the 70- to 80-hour weeks and long week-ends their predecessors did. The new physician is surrounded by the 40-hour week, by every third week-end on duty, and by all the usual habits of his or her friends, and such habits will rub off.

4) Many more physicians will be involved in administration and industrial positions than at present.

The young woman and young man who want to study medicine today should have the same opportunities their predecessors had 30 to 40 years ago. If those already in practice perceive that there are enough or too many physicians, they still have no justification for denying access to their profession by as many young persons as want to consider a medical career. And who can predict with certainty what the needs will be 20 years from now?

The practicing neurosurgeons of the United States, represented by the Joint Socio-Economic Committee of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons have repeatedly stated that there are too many neurosurgeons and that we should cut back on the number of neurosurgical residencies in this country. They have called on the American Association of Neurological Surgeons to cut back on that number. This is simply one example of a small specialty that is seeking to have control from above.

Other groups have implored the AMA to "do something about the surplus of physicians." Some physicians who know little of the legal aspects of accreditation consider the Liaison Committee on Medical Education to be the proper agency through which to cut down on the number of persons being admitted to medical school.

It is well to remember that we have had a large increase in the number of 22-year-old college graduates since 1965. The number of applicants to medical schools of the United States has closely paralleled that number of 22-year-old graduates for the past 55 years. If there had been fewer openings in medical schools over those years, more American college graduates would have had to seek medical training abroad. Now, however, the number of 22-year-old college graduates is declining, and the cost of an education is increasing, not only for the student but for the governing institutions — in many instances, the governing institutions being the individual states. The state legislators hear from the GMENAC (Graduate Medical Education National Advisory Committee) report that we have or will have too many physicians and they find themselves under pressure from their constituents and fellow legislators to save precious tax dollars by decreasing (or at least not increasing) the support to state medical schools.

The number of graduates of medical schools in America will almost certainly diminish, since no new schools are in formation, and many schools have already reduced the size of their entering classes. With the drop in the number of 22-year-old graduates, state schools that largely limit their admissions to students from that state are finding a smaller and sometimes less well-qualified pool of applicants.

The American Medical Association, the Association of American Medical Colleges, the Liaison Committee on Medical Education or even a specialty organization such as the American Association of Neurological Surgeons — none of these or similar organizations can determine the number of graduates from medical school or the number of physicians being trained in their specialty except on the basis of quality, which must always be justified.

Rather, the market place and the judgment of individual students in deciding on a medical career should best decide how many first-year medical students we have. States will decide on the number of students to be admitted to the schools they support, depending on the number of physicians needed and the funds available.

As for the students who choose to go abroad for their training in medicine, there can be no control over their numbers except by the State Department, possibly by the General Accounting Office, or by some other Federal Agency. But for their return to obtain graduate training and licensure here, there will be control on the basis of quality by the Accreditation Council on Graduate Medical Education and on the basis of law by the State Boards of Medical Examiners. The Federation of State Medical Boards has made strenuous efforts to obtain information about foreign medical schools to aid the individual state boards of medical examiners in making the appropriate decisions. This is a sincere effort to maintain the quality and high standard of medical practice in America, and is a better means of controlling the "doctor glut" than trying to limit the number of persons obtaining a medical degree because those in practice perceive we have too many.

N. B. The already-employed taxi drivers in San Francisco recently launched a horn-blowing protest before the Mayor's office to keep her from issuing additional licenses to drive cabs in preparation for the Democratic National Convention in July '84. Similar??

From Dr. W. G. Anlyan, Chancellor for Health Affairs in Durham.

It is a three layered problem: 1) American and Canadian schools; 2) USFMGs educated in the Caribbean and elsewhere abroad; 3) alien FMGs, particularly those from developing nations.

Regarding layer #1, I believe we have overbuilt the number and size of American medical schools. I cannot comment on the Canadian schools since presumably they serve primarily the needs of Canada. Layer #2 is uncontrolled since they are not accredited by the liaison committee on medical education. We don't know the exact size of the pool. The quality varies from diploma mills to more organized medical schools. If left to individual states to license these graduates, there is no question that states like New York will be more lenient not only because of the needs of their governmental and municipal hospitals, but also because the political clout of the parents of the students is tremendous. As a matter of fact, I learned in New York recently that Governor Cuomo had as one of his top priorities to build a medical school in Queens. It was a political pledge. He will undoubtedly absorb most of the class from Granada. It is probable that the City University of New York will be charged with running it. Layer #3, to put a quota on the admission of alien FMGs, has been suggested by GMENAC. The federal legislation which was submitted was defeated by states such as New York.

The only possible combination of solutions would be as follows:

A. For the U.S. medical schools to cut back on their enrollment on a voluntary basis rather than by a federal edict.
B. To require one or two years of an approved residency training program on a national basis as a prerequisite to obtaining licensure in all 50 states.

Keep in mind that the physicians entering practice in 1984 will on the average have graduated from medical school in 1976 before the development of the major bulge in enrollment. The big bulge is yet to come and will probably hit in the period between 1990 and the year 2000.

From Dr. George W. Crane, Jr., a dermatologist in Durham.

Is there a doctor glut? In the rural areas, no; in the urban areas, yes.

Durham County General Hospital has 462 beds available at this time, and lists 240 physicians on the medical staff, roughly 2 patients per doctor.

Many nondermatologists are treating dermatologic problems due to competition for patients, or because they feel comfortable dealing with them after a brief course or preceptorship in dermatology.

Duke and University of North Carolina each has 3 residents completing the dermatology program every year and many establish practices in this and the surrounding areas.

In the past 7 years the above factors have reduced our patient load to the point that two dermatologists can handle a practice that formerly required 3.

Evening and Saturday office hours are once again available in some private practices.

Suggested methods to correct surplus:

Medical school enrollment reduction: State and county medical societies may be required to urge state and Federal legislatures to stop spending tax money to subsidize the medical schools on a per student basis. With the exception of a few schools, such as Duke, this move is unlikely to be initiated by the school due to a loss of income.

Limit the number of Americans who train in foreign medical schools and return to the United States to practice.

Foreign-born, foreign-trained physicians taking post-graduate training in the United States should return to their home country or have legal restrictions on licensure even if they marry an American, or have children born in the United States.

From Dr. John R. Gamble, Jr., a general surgeon in Lincolnton.

As a practitioner in an average rural North Carolina county I have not experienced a doctor glut. I know that we will continue to need replacement physicians, new physicians to meet population and increasing utilization needs, and new physicians with specialty and sub-specialty skills. Our county population has increased forty to fifty percent in the past twenty years and our physician population has more than doubled and we are actively recruiting physicians. I feel that any patient who feels the immediate need of physician care should have access to that level of care and that a patient who seeks an appointment should find one available in no less than three or four days.

Should others disagree on the doctor glut I feel that the key point is not to over react and cut back on the educational opportunities of our state's own citizens and thus continue the influx of foreign national physicians. Organized medicine must get its facts and plans organized to insist that the United States Immigration Service not continue its policies of bringing in foreign physicians as a detriment to the opportunities of our state's citizens. I personally feel that our state and other states have the obligation to provide the educational opportunities to their own young people and thus fulfill the expectations to which they are entitled and not default on this responsibility by allowing career openings to be filled by physicians from other countries.

From Dr. G. Radford Moeller, an internist in Pollocksville.

In 1969, as I contemplated a career in medicine, a wave of opinion was cresting in this country which contended that a significant shortage of doctors existed in America. Some individuals even purported to say that a "crisis situation" existed. Others were skeptical, stating that no shortage existed and that a redistribution of physicians could rectify the perceived short fall of health care providers.

In 1973, when I entered medical school at Duke, I discovered that the size of my class was significantly greater than preceding classes. This fact seemed to validate the concept of the "doctor shortage."

In 1982, however, as I eagerly sought a challenging position as a Rheumatologist in private practice, I discovered that an amazing proliferation of sophisticated, subspecialty medicine had quietly occurred in North Carolina. Cities which had no Rheumatologists when I began my fellowship had, in many cases, more than one by 1982.

At Craven County Hospital in New Bern, there were but approximately 25 physicians in 1970. Today there are in excess of 100. Yet during that same period, the population of Craven County increased less than 10%. I know of no physician at our hospital who feels underutilized. How can a stable population support such a dramatic increase in the size of a medical staff?

I believe that just as NMR and CT scanners have failed to replace older, more traditional, diagnostic tests, the arrival of subspecialists in the many disciplines of medicine previously not represented in our community has provided talents which, in most cases, do not directly duplicate those of the existing physicians. In this sense, then, there is no "doctor glut" in New Bern in 1984

However, there obviously is an end point past which such phenomenal growth will result in an underutilization of physicians. I believe that as New Bern and most towns in North Carolina rapidly reach a condition in which virtually all subspecialties of medicine are represented, a necessary reduction in the rate of growth of the physician pool will have to be instituted. If this does not occur, the "doctor glut" created will surely impose a counterproductive, overly competitive practice environment, which I believe will both increase the total cost of delivering quality health care to our patients and serve to undermine many of the moral imperatives that have to date directed our practice of medicine.

I believe that steps must be taken to avoid a needless, wasteful "doctor glut." Medical schools should be induced to reduce the size of their entering class to original pre- "doctor shortage" levels. The ease with which certain Americans, unsuccessful in their attempts to gain admission to American medical schools, are able to return to practice in North Carolina after obtaining the MD degree (often in the Caribbean and Mexico) needs reevaluation. Steps should be taken to ensure that foreign graduates of foreign medical schools who seek subspecialty training in the United States, often unavailable in their home country, are encouraged to return to their native countries — thus providing for the intended dissemination of medical techniques and knowledge.

I suspect that any attempt by a physician organization to encourage and implement such maneuvers will be viewed as a monopolistic giant attempting to protect its self-serving interests. Medicine has no shortage of biased critics today. Therefore I would advocate that the burden of implementing these measures should fall correctly upon those who, among others, argued so forcefully in favor of an expansion of the physician supply in the 1960s, the State and United States legislatures.

In 1984, in Pensacola, Florida, physicians solicit patients through the use of roadside billboards and immodest telephone yellow page advertising. These outward evidences of the "doctor glut" there only allude to other dramatic, negative departures from the traditional style and code of medical practice fostered by the unfortunate influences of excessive competition. I believe the rate of growth of the physician pool in North Carolina must be reduced if we are to avoid the "doctor glut" and its detrimental

consequences for both our patients and ourselves.

From Dr. John W. Watson, a family practitioner in Oxford.

The doctor glut has not yet arrived in Granville County or in any other rural county, I suspect. If one were to ask this question of my fellow physicians, the answers would vary depending on the physician and his specialty. For example, surgeons do not feel that there is a need for more surgeons but do think there is probably room for more internists and family practitioners; conversely, internists and family practitoners might disagree with the notion that more of themselves are needed.

When I came to Granville County almost 30 years ago, there were 19 physicians none of whom were board certified in any specialty except the radiologist whom we shared with three other communities. The surgery, obstetrics, anesthesia, and general medicine were all peformed by general practitioners. The emergency rooms of two hospitals, one black and one white, were covered full time by these physicians. There were approximately 120 beds total in the two hospitals whereas today there is one hospital with 62 beds. Included in those 19 physicians were two black physicians. There were no female physicians and no graduates of foreign medical schools.

Today we have 14 full time doctors of whom eight are now in family practice and most board-certified; there are two internists, one board-certified and one board-eligible; there are two board-certified general surgeons, one board-certified gynecologist, one board-certified radiologist, and one board-eligible psychiatrist. In addition, there is a urologist shared with another community, a rural health clinic with a family nurse practitioner and physician's assistant, and an office that three out-of-county physicians staff which is equal to one full-time physician. There is also approximately three-fourths coverage of our emergency room contracted with an emergency room service.

The physician population today has other differences from that of 30 years ago. Two of our current doctors are United States citizens who graduated from foreign medical schools. Two more are immigrants who are graduates of foreign medical schools, and our shared urologist is also an immigrant who was educated abroad. We have one black full-time physician, and three physicians sharing one office on a part-time basis are black. We also, last but not least, have one female physician, a psychiatrist.

The population base from which our patients are drawn has decreased somewhat over the past 30 years although the total county population has increased. There are a variety of reasons for this, mostly related to geography, to improved highways, and to the improved technology in medical care.

We now have approximately the same physician-to-patient ratio that we did 30 years ago; however, our make-up is entirely different and we offer more services. The years in between now and 30 years ago were sometimes very difficult with only seven or eight full-time physicians covering emergency rooms, delivering babies, and generally staying full-time fatigued.

No, there is not glut of doctors in Granville County now. In the event such a glut should develop, which I feel is unlikely, the only recourse would be for medical schools to cut class sizes and/or for states with many schools to consolidate them. Two factors will work against a glut of physicians in active practice. The medical schools have increased the percentage of female students to 30-40% of their class. It is probable that many of these physicians will at least have periods in their professional lives when they will not be in active practice or only in part-time practice similar to what has happened with registered nurses. Another factor is that of earlier retirement for physicians. In the past, physicians have pretty much died with their boots on; however, with a more plentiful supply of physicians, they are more likely to retire earlier, particularly if they are able to sell their practices while they are still flourishing.

If a glut of physicians does develop, then I believe that the practice of medicine will change drastically with all sorts of entrepreneurs becoming involved in medical care and all of us will suffer — patients and physicians.

• EDITOR'S NOTE: I am delighted by the response to our first question of the month. Thank you for your opinions.

Health manpower needs and the "doctor glut" are extremely important issues. Obviously there are many different currents of thought concerning whether or not the problem exists and, if so, what to do about it. The responses in this issue of the *Journal* illustrate some of these currents.

Two recent articles in *The New York Times* also illustrate some of the controversy. In an article published on April 4, Ronald Sullivan reported that the New York State Health Department would begin to enforce a law barring American students enrolled in "unapproved" foreign medical schools from completing their medical education in New York State teaching hospitals. (In 1981 the State Board of Regents in New York had set up a system of inspecting and approving off-shore schools.) In a later article (April 18) the same reporter stated that another medical school would soon be opening in New York City to graduate more black and Hispanic physicians.

North Carolina Medical Journal

Features for Patients June 1984

Stepped Care for Diabetes Mellitus

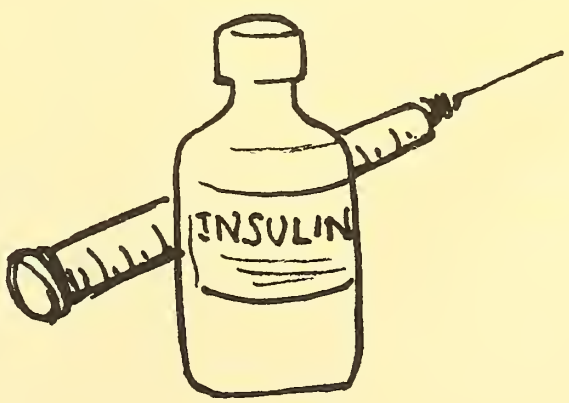
Geo. J. Ellis, M.D.

This orticle is pure opinion, with no data to confuse anyone. It may be useful for people with diobetes trying to decide just how they would like to structure their medical core, and for physicions and other health care providers trying to evolve more effective ways of deoling with diobetes mellitus — o common condition thot requires o different opproach from most others. It is the viewpoint of a consultont seeing potients who want better diobetes monogement ond who ore seeking a speciolist with the hope thot he con help them. If *you* have diabetes, you may see the condition os resembling o 50% surchorge on your tox bill (ond if you don't pay it, we'll kill you!). It's simply unfoir for you to be selected by the gods to hove diobetes. You moy hove o voriety of *feelings* obout it, such os onger, sodness, or frustrotion; but whot you *do* obout it is up to you. If those feelings keep you from coring for yourself os you feel you should, tell your doctor. S/he may be oble to help you talk through those feelings or orrange for counselling if oddition-ol help is needed.

What is diabetes?

Whot you ore deoling with is on inherited or ocquired defect in insulin secretion or oction. Lock of insulin effect meons glucose cannot enter cells efficiently, causing blood sugar levels to rise — often to the point thot the kidney can no longer solvoge oll the filtered sugor — ond you woste sugor, woter to dissolve it, ond minerols into the urine. When control is very poor, high sugor levels con drow woter from the brain and impoir consciousness. By this point, body cells are starved for the energy normolly provided by glucose (the mojor blood sugar). The energy shortage is helped by breoking down fot into smoll porticles (short chain fatty acids ond ketones). More smoll frogments ore mode thon the body con burn. This excessive production moy leod to *diobetic acidosis*, o life-threotening emergency.

With treotment, diabetes can be controlled, but often not perfectly. It's easiest to bolonce diet, exercise, ond insulin well enough to ovoid ketoocidosis and coma. But even modest elevations in blood sugar over many yeors are thought to increase the risk of long term complicotions of diobetes such as blindness, poinful nerve damage, ond kidney foilure. We have increasingly cleor notions of *how* elevoted blood sugors moy be linked to the chronic complicotions. We now believe thot even these complicotions moy be ovoided or minimized — in some who seem luckily protected from developing them, and



From the Division of Endocrinology ond Metabolism, 2924 Duke Hospitol, Durhom 27710.
Illustrations by Ernest Croige, M.D.

in others — by maintaining very precise cantral of blaad sugar ta near narmal levels. It seems best always ta have narmal blaod sugors, but any impravement, even after years of poar cantrol, may lower future risks.

Control Strategies

Contral may be ochieved by a series af strategies that may have o small to intalerably great impact an yaur life style. Mast impartant is o meal plan, composed af a balanced and whalesame variety af foods. Meats and other faads are chasen ta maderote chalesterol and saturoted fat intake. Breads and vegetables that contain camplex carbahydrates and that are rich in fiber are best ta smooth the fluctuations in blaad glucase. Meal planning using "exchanges" of comparable foods encaurages variety and flexibility while maintaining a stable calaric intake and an even distribution of fat, carbohydrate and pratein. Rapidly absarbed simple sugars are minimized. Three to six feedings daily help spread faad absarptian to match needs and insulin effect. This amounts ta the sart af diet an early settler in this area might have chosen spantaneausly, but far a generatian used ta canvenience and junk foads, the change can be a shock! Regular exercise is impartant in achieving full insulin effectiveness. It may be as simple as walking one to five miles daily, or you may seek odditianal benefits fram more vigoraus "conditianing" levels af exercise like jagging ar bicycling.

When these meosures fail to achieve normal blaad glucase, agents to lawer blaad sugar may be prescribed. Thase wha can make *part* af their insulin requirement may respand to pills which may help the bady to praduce mare insulin ond/or make the available insulin work better. Others may require replacement af insulin, which must be injected at least daily. Unlike some medicotians, which are aptimally distributed by the body with infrequent dases, insulin is difficult to deliver with the praper timing. Normally, insulin increases in the blood after eoch feeding, and — ta avaid law sugars (hypaglycemio) — should foll to lower levels during exercise and befare feedings. Such reductions in insulin levels are impassible ta ochieve with

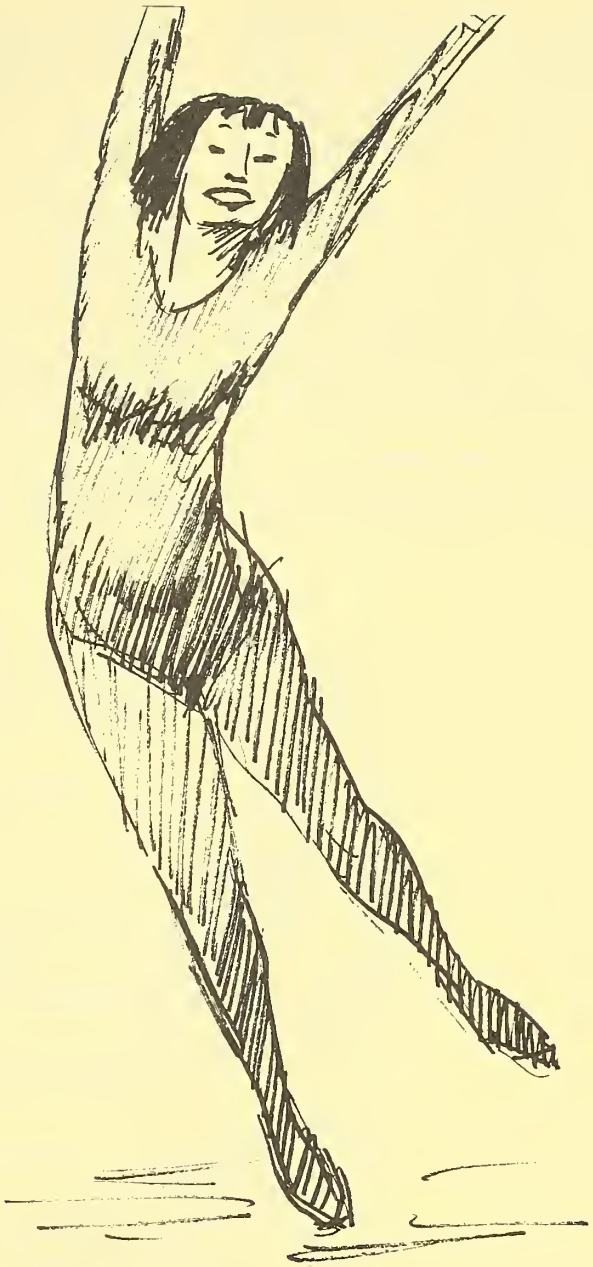
. . . a generation used to convenience and junk foods . . .



o single doily injection of insulin when the potient is unoble to produce ony insulin. If the insulin dose is then increosed until some "torget" blood sugor (commonly before breokfost) is normol, there is often excessive insulin ot other times — especiolly during the night. This couses low blood sugor (hypoglycemio) which moy be felt os unpleosont hunger, sweoting, tremor, ond ropid heort beot. In severe "insulin reoctions" there is o risk of seizures, unconsciousness, broin domoge, ond even deoth. When optimol control follows o single doily injection of insulin, it is becouse the potient, once provided enough "bosol" insulin to lower fosting blood glucose to normol, is oble to produce enough short octing insulin to motch feedings. Others moy require two to four injections or even o pump to motch insulin levels to the body's needs.

Which doctors can help?

Choosing how to monoge your diobetes — ond whot doctor to odvise you — is difficult. You should consider your gools. Do you simply wont to expend the leost energy to stoy out of the hospitol? Will you do *onything* to preserve your heolth? Review your resources for deoling with diobetes, including time, obility to leorn, support for expenses, ond help from your fomily. In ony cose, most will begin with o primory core physicion, usuolly o fomily physicion, pediotricion, or internist, ond often the doctor who helped you estoblish the diognosis of diobetes. The time to consider consultotion is when you ond your physicion ore unoble to ochieve the control you desire despite your best efforts. A consultont in diobetes moy well be troined in greoter depth with respect to diobetes thon your primory physicion. However, s/he will generolly mointoin this expertise ot the expense of generol medicol knowledge. So it moy be wise to rely on your primory physicion to support your diobetes progrom ond to deol with other problems even while you ore seeing o speciolist obout your diobetes. This orrongement, *consultotive monogement,* moy prove both sofer ond more economicol for you. When your diobetes control hos reoched the optimol level, you moy be oble to mointoin it with the ossistonce of your primory physicion, using your consulting speciolist for unusuol problems os needed.



regular exercise is important

New Roles for You and Your Doctor

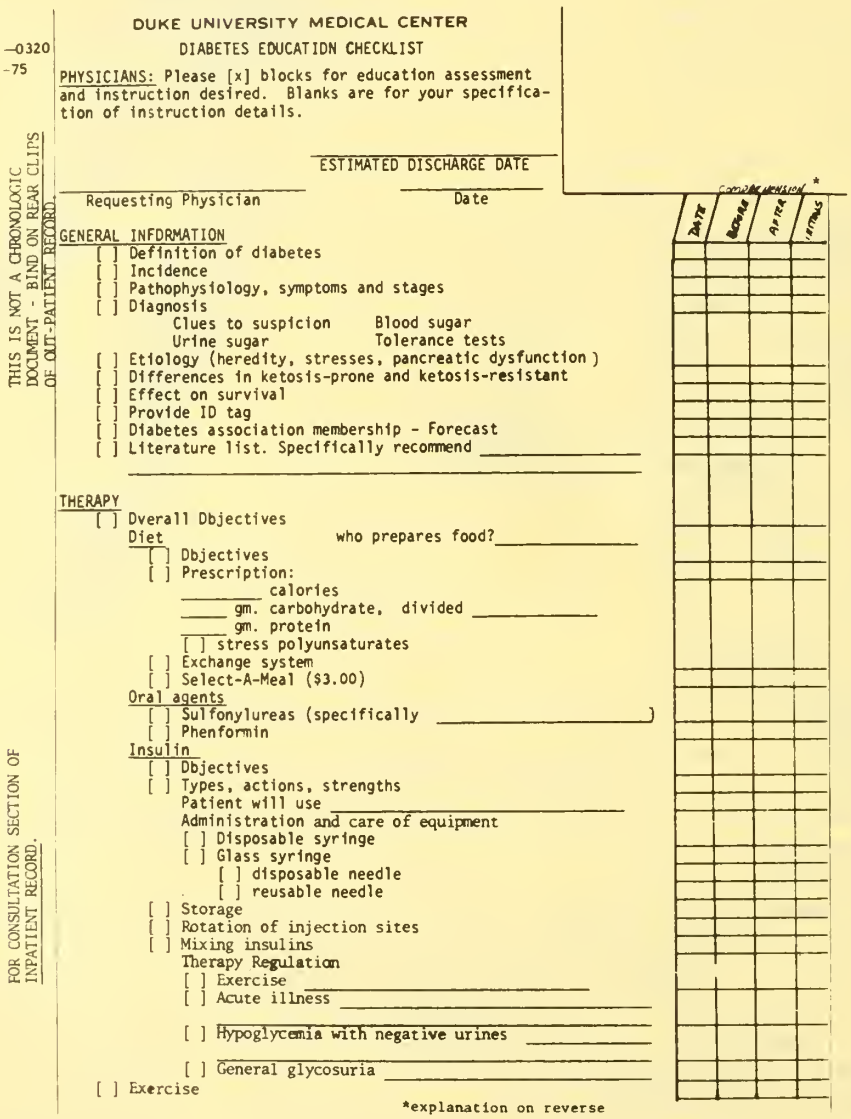
Your role in monoging diobetes is different from your role in other more ocute heolth problems. Rother thon simply follow o routine prescribed by your doctor, it moy be best for you to toke over the doy to doy odjustments required for optimol control. You

adopt the dactar's usual role af "playing the game" ta achieve the best results far your health. Your dactor then becomes the "coach" who helps yau win the game. With this level af responsibility, you will require a mare tharaugh educatian than is necessary ta get aver pneumania. Your diabetes physician and his staff can provide this, alang with a step-by-step appraach to therapy thot will allaw yau ta achieve yaur gaal level af cantrol as easily as passible.

Diabetes Education

Figures 1 ond 2 are an abbrevioted outline af passible elements of a "camplete" diabetes educotion fram which the physician can specify chaices appropriate for an individual patient. Same patients will have achieved the fullest practical education with three ar faur items; athers, with unstable diabetes, may need ta master most areas far aptimol cantral. If yau encaunter oreas an the checklist you feel wauld be helpful in your awn monagement, discuss them with yaur physician. Mast af the GENERAL INFORMATION items are self explanatary. We da recammend joining a local diabetes assaciatian (See "American Diabetes Assaciatian of Narth Carolina, Inc." in larger telephone directaries statewide) and reoding *Diabetes Forecast* magazine (pravided with yaur membership) to help with keeping up abaut diabetes. Literature must be provided ta satisfy individual needs, but Luther Travis' *Guide* explains many of the necessary concepts lucidly and accurately.[1]

THERAPY educatian returns to the familiar triad af diet, exercise, and hypaglycemic therapy. Yaur meal plan prescriptian is optimally designed to achieve and maintain ideal weight and ta minimize swings in blaad glucose during the day. There may be special recammendatians regarding fat cantent and sadium or



DUKE UNIVERSITY MEDICAL CENTER

DIABETES EDUCATION CHECKLIST

—0320
-75

PHYSICIANS: Please [x] blocks for education assessment and instruction desired. Blanks are for your specification of instruction details.

THIS IS NOT A CHRONOLOGIC DOCUMENT - BIND ON REAR CLIPS OF OUT-PATIENT RECORD.

ESTIMATED DISCHARGE DATE

Requesting Physician _____ Date _____

Completion *

DATE | DOSAGE | NURSE | INITIALS

GENERAL INFORMATION
- [ ] Definition of diabetes
- [ ] Incidence
- [ ] Pathophysiology, symptoms and stages
- [ ] Diagnosis
  - Clues to suspicion
  - Blood sugar
  - Urine sugar
  - Tolerance tests
- [ ] Etiology (heredity, stresses, pancreatic dysfunction)
- [ ] Differences in ketosis-prone and ketosis-resistant
- [ ] Effect on survival
- [ ] Provide ID tag
- [ ] Diabetes association membership - Forecast
- [ ] Literature list. Specifically recommend _____

THERAPY
- [ ] Overall Objectives

Diet — who prepares food? _____
- [ ] Objectives
- [ ] Prescription:
  - _____ calories
  - _____ gm. carbohydrate, divided _____
  - _____ gm. protein
  - [ ] stress polyunsaturates
- [ ] Exchange system
- [ ] Select-A-Meal ($3.00)

Oral agents
- [ ] Sulfonylureas (specifically _____)
- [ ] Phenformin

Insulin
- [ ] Objectives
- [ ] Types, actions, strengths

Patient will use _____

Administration and care of equipment
- [ ] Disposable syringe
- [ ] Glass syringe
  - [ ] disposable needle
  - [ ] reusable needle
- [ ] Storage
- [ ] Rotation of injection sites
- [ ] Mixing insulins

Therapy Regulation
- [ ] Exercise _____
- [ ] Acute illness _____
- [ ] Hypoglycemia with negative urines _____
- [ ] General glycosuria _____

[ ] Exercise

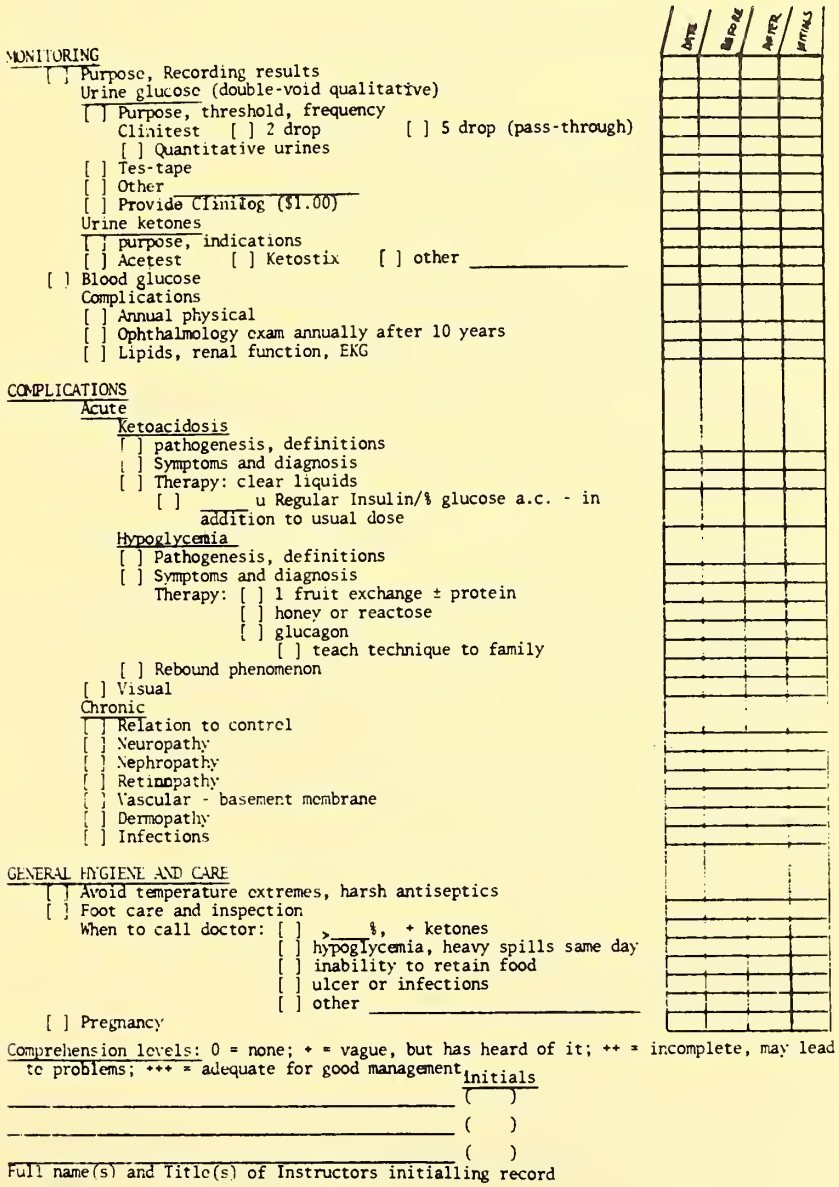
FOR CONSULTATION SECTION OF INPATIENT RECORD.

*explanation on reverse

Figure 1. Side 1 of the Duke Diabetes Education Checklist.

salt content. Although it may seem strange and new to you, your meal plan can be varied and palatable. If you have not found this to be the case, remember that a dietician can provide numerous cookbook and recipe suggestions to supplement the basic American Diabetes Association meal planning booklet. If you use oral agents, you will want to understand their advantages and potential risks. These medications are effective only in combination with a careful meal plan. One risk of the oral agents is hypoglycemia, which is especially likely if other medications are taken which can displace the oral agent from storage on blood proteins, increasing their glucose-lowering effect. Hypoglycemia caused by oral agents may last several days and often warrants hospitalization. It is wise to ask your doctor and pharmacist about such potential drug interactions whenever you are prescribed a new medication. Such hypoglycemia may also follow use of over-the-counter medications (especially those containing aspirin), so check these out as well. The greatest advantage is that a few patients can achieve continuously normal blood glucose control much more easily than they could with injected insulin; this is because they are using their built in glucose monitoring ability and can release some insulin with each feeding. Thus oral agents *may* be more effective than injected insulin in helping your body approach normal physiology.

We instruct most patients in using injectable insulin, even when they may not require it daily. During an illness, insulin requirements may rise so that a purified insulin must be used temporarily to maintain control. Maintaining control during illness helps you to heal more effectively, prevents symptoms from the diabetes itself, and reduces the risk of "islet cell decompensation," or impairment



MONITORING
- [ ] Purpose, Recording results
- Urine glucose (double-void qualitative)
  - [ ] Purpose, threshold, frequency
    - Clinitest [ ] 2 drop [ ] 5 drop (pass-through)
    - [ ] Quantitative urines
  - [ ] Tes-tape
  - [ ] Other _____
  - [ ] Provide Clinitog ($1.00)
- Urine ketones
  - [ ] purpose, indications
  - [ ] Acetest [ ] Ketostix [ ] other _____
- [ ] Blood glucose
- Complications
  - [ ] Annual physical
  - [ ] Ophthalmology exam annually after 10 years
  - [ ] Lipids, renal function, EKG

COMPLICATIONS
- Acute
  - Ketoacidosis
    - [ ] pathogenesis, definitions
    - [ ] Symptoms and diagnosis
    - [ ] Therapy: clear liquids
      - [ ] _____ u Regular Insulin/% glucose a.c. - in addition to usual dose
  - Hypoglycemia
    - [ ] Pathogenesis, definitions
    - [ ] Symptoms and diagnosis
      - Therapy: [ ] 1 fruit exchange ± protein
        - [ ] honey or reactose
        - [ ] glucagon
          - [ ] teach technique to family
    - [ ] Rebound phenomenon
  - [ ] Visual
- Chronic
  - [ ] Relation to control
  - [ ] Neuropathy
  - [ ] Nephropathy
  - [ ] Retinopathy
  - [ ] Vascular - basement membrane
  - [ ] Dermopathy
  - [ ] Infections

GENERAL HYGIENE AND CARE
- [ ] Avoid temperature extremes, harsh antiseptics
- [ ] Foot care and inspection
- When to call doctor: [ ] >____%, + ketones
  - [ ] hypoglycemia, heavy spills same day
  - [ ] inability to retain food
  - [ ] ulcer or infections
  - [ ] other _____
- [ ] Pregnancy

* Comprehension levels: 0 = none; + = vague, but has heard of it; ++ = incomplete, may lead to problems; +++ = adequate for good management

Initials

_____ ( )

_____ ( )

_____ ( )

Full name(s) and Title(s) of Instructors initialling record

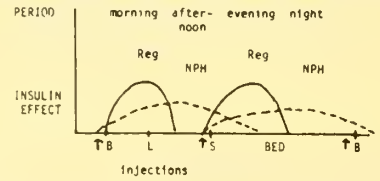
Figure 2. Side 2 of the Duke Diabetes Education Checklist.

of the ability to produce insulin caused by very high blood sugars continuously stimulating the pancreatic islets. Because of the "dead space" in syringes with detachable needles, disposable syringes are recommended for those who mix insulins. If economy is important, you may reuse these safely several times. Insulin in use may be stored at comfortable room temperatures without loss of potency. Since we learned of the different rates of absorption of insulin injected into different sites, we have suggested rotation within regions before moving to a distant site. A patient with two daily injections might take the morning injection in the arm or abdomen (which more quickly release the insulin into the blood) and the afternoon injection in the leg or buttock. Exercise of an extremity also increases absorption, so we avoid injecting the leg just before running.

I believe it is more efficient for patients to adjust their own insulin doses when they can do so safely and comfortably. Changes in *basal dose* can be specified by an *algorithm* (a rule for making adjustments) such as the one in figure 3. Such algorithms are available for most common insulin regimens. This introduction of the concept of *feedback regulation* into the life of the person with diabetes represents an important advance over having the doctor make all the decisions. The decisions become more

M-07095
Rev. 3-83

ADJUSTING INSULIN DOSES USING A "SPLIT-AND-MIXED" REGIMEN



ASSUMPTIONS

The morning short-acting insulin (REGULAR, SEMI LENTE, or ACTRAPID) has major action between breakfast and lunch, and its effect is reflected in the test results *before lunch*.

The morning intermediate-acting insulin (NPH, LENTE, or MONOTARD) has major action between lunch and supper, and its effect is reflected in the test results *before supper*.

The evening short-acting insulin has major action between supper and bedtime, and its effect is reflected in the test results *at bedtime*.

The evening intermediate-acting insulin has major action overnight, and its effect is reflected in the test results *before breakfast* the next day.

HYPERGLYCEMIA (HIGH BLOOD SUGAR) NOT EXPLAINED BY UNUSUAL DIET/EXERCISE/INSULIN

If urine sugars are *positive* or if blood glucose is *over 140 mg/dl* for ____ days in a row *before lunch*, beginning on day ____ *increase* your morning REGULAR (or SEMI LENTE, ACTRAPID) insulin by _____ units.

If urine sugars are *positive* or if blood glucose is *over 140 mg/dl* for ____ days in a row *before supper*, beginning on day ____ *increase* your morning NPH (or LENTE, MONOTARD) insulin by _____ units.

If urine sugars are *positive* or if blood glucose is *over 140 mg/dl* for ____ days in a row *at bedtime*, beginning on day ____ *increase* your evening REGULAR (or SEMI LENTE, ACTRAPID) insulin by _____ units.

If urine sugars are *positive* or if blood glucose is *over 140 mg/dl* for ____ days in a row *before breakfast*, beginning on day ____ *increase* your evening NPH (or LENTE, MONOTARD) insulin by _____ units.

HYPOGLYCEMIA (LOW BLOOD SUGAR) NOT EXPLAINED BY UNUSUAL DIET/EXERCISE/INSULIN

For *hypoglycemic reactions* or blood glucose measurement *under 70 mg/dl* occurring *between breakfast and lunch*, reduce your next morning's REGULAR (or SEMI LENTE, ACTRAPID) insulin by _____ units.

For *hypoglycemic reactions* or blood glucose measurement *under 70 mg/dl* occurring *between lunch and supper*, reduce your next morning's NPH (or LENTE, MONOTARD) insulin by _____ units.

For *hypoglycemic reactions* or blood glucose measurement *under 70 mg/dl* occurring *between supper and bedtime*, reduce your next evening's REGULAR (or SEMI LENTE, ACTRAPID) insulin by _____ units.

For *hypoglycemic reactions* or blood glucose measurement *under 70 mg/dl* which occur *overnight*, reduce your next evening's NPH (or LENTE, MONOTARD) insulin by _____ units.

Figure 3. An olgorithm for odjusting insulin doses for patients using two injections of mixed insulin (a split-ond-mixed regimen). The clinicion tailors these guidelines for an individuol patient by specifying the frequency ond omount of dose odjustment to be mode by the potient. Note that urine ond/or blood glucose results moy be employed. Errors in dose odjustment may be detected by the clinician ot o periodic visit by review of o properly completed diobetes log.



monitoring diabetes makes sense

timely, ond potients seem more willing to gother doto for their own immediote use thon for the doctor's loter review. All components of theropy moy need to be reguloted for unusuol exercise (less insulin ond/or more food), ocute illness (more polotoble food, supplements of short octing insulin; we provide *Sick Day Guidelines* to exploin this oreo in detoil), chonges in work shift, menstruol periods, or trovel.

MONITORING diobetes mokes sense to potients who use the informotion doily to moke odjustments in theropy. Checking urine glucose remoins the leost expensive method, ond con give excellent control in potients who spill glucose into the urine when the blood level of glucose is only moderotely elevoted ond who olso recognize the symptoms of hypoglycemio occurotely before the blood glucose folls so low thot judgment is impoired. Those who continue to moke some insulin in response to feeding moy ochieve normol blood glucoses ot oll times without monitoring blood glucose. The glucose oxidose strip methods ore convenient ond sensitive for those who rorely hove positive urine sugor. The 2-drop Clinitest ond Chemstrip μG methods ore excellent for those who need to somple the ronge of 0-5% sugor. Self monitoring of blood glucose is recommended for those with on obnormol threshold, feor of — or inobility to recognize — hypoglycemio, unusuol instobility, pregnoncy or odvoncing complicotions (worronting intensive efforts to improve control), or potient preference. Severol visuol strips ond severol meters give quite comporoble results (occurocy ±15%) provided technique is meticulous. It is importont thot eoch potient volidote his occurocy with loborotory comporison ofter detoiled instruction. Figures 4 ond 5 show two populor logs for recording these results. They fit eosily into o pocket or purse, ond ore orronged so thot persistent elevotions in glucose ot o given time of doy ore reodily recognized. It's o good ideo to record ony chonge in insulin dose in your log *when you record the test result* leoding to the chonge. It seems eosier to forget the odjustment if one woits until time for the next injection.

Periodic meosurement of glycosyloted hemoglobin by the physicion

Month		Urine Sugar/Ketone (Acetoacetic Acid)								Medication		How Do I Feel Today?
Date	Day	A.M.		NOON		P.M.		BED				
		Sugar	Ketone	Sugar	Ketone	Sugar	Ketone	Sugar	Ketone	Dose/Time	Dose/Time	
1												
2												
3												
4												
5												
6												
7												

Figure 4. The *Clinilag* was developed by the Ames Company and is available via local pharmacies from Ames Clinilog II, Box 9706, St. Paul, MN 55197. Individual copies may be ordered for $1 from Ames Clinilag II, P.O. Box 802, South Bend, IN 46624. Two weeks' results may be viewed at once. Although designed for urine sugar monitoring, it will accommodate blood glucose results or a mixture of urine and blood sugar recording in the generous blocks. It is important to record insulin dose at the top of each page, and again if there is a dose change. There is space for recording the time of hypoglycemia, unusual exercise, illness, stress, or other factors that may have altered control.

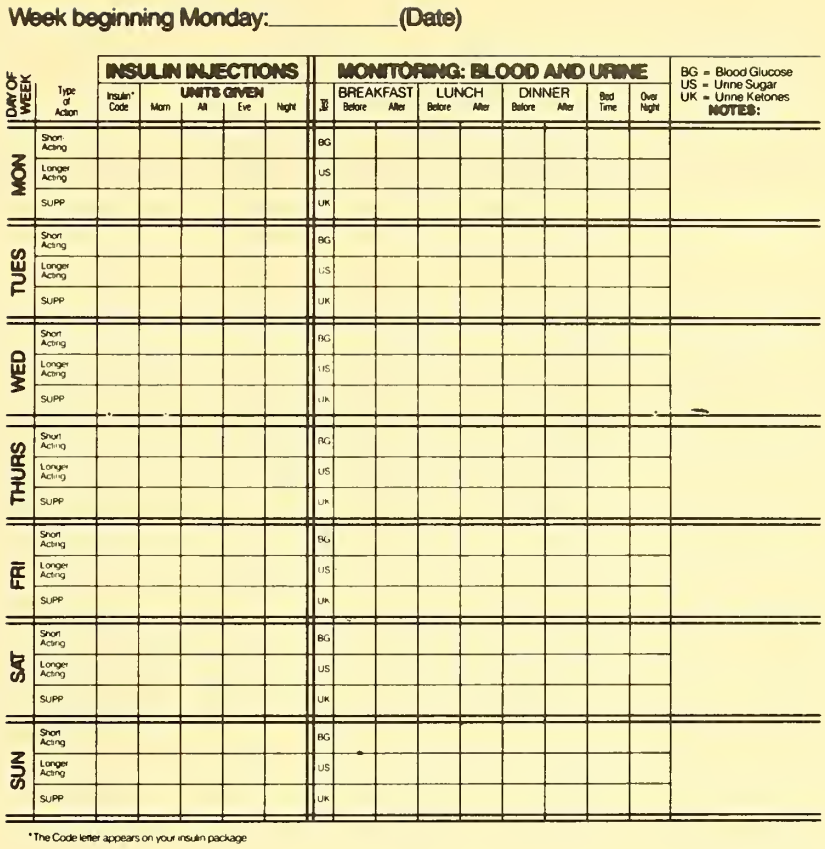
provides on additional check on self monitoring. This assay measures the fraction of hemoglobin in the red blood cells that has had sugar attached. This chemical reaction occurs in proportion to the blood glucose levels, so the assay estimates average blood glucose levels over a two month period. The test can provide useful confirmation of patient data. A marked *discrepancy* of glycohemoglobin result from glucose data is even more helpful because it provides new information. When urine or blood glucose results are known to be elevated, yet glycohemoglobin is normal or low, the explanation is often *unrecognized* hypoglycemia, most commonly during sleep. On the other hand, glucose estimates by the patient may be close to normal. In this case a markedly elevated glycohemoglobin may indicate invalid home testing from faulty technique, defective test materials, or recording fraudulent test results. We also recommend checking urine acetone at least before breakfast daily, regardless of the glucose result at the time. Ketones are produced when body cells are starved for sugar. You are familiar with ketone production during severe insulin deficiency (ketoacidosis). Missing meals also increases ketone production. When you are eating according to plan, a positive test for ketones when glucose is *not* elevated may provide a clue to earlier unrecognized hypoglycemia. Remember that ketones are produced in three *different* settings — insulin deficiency, lack of food, and insulin excess.

COMPLICATIONS are included in education so that they may be recognized and dealt with, or even avoided. Likewise, proper foot care, and knowing how and when to reach your doctor may help you avoid a prolonged hospitalization.

Contracts, Goals, and Problems

The treatment you receive for your diabetes must be the result of an understanding between you and your doctor about 1) how well you are doing as compared with your goals for control and 2) how hard you are willing to work to achieve control. If you feel well and most of your urine and/or blood glucose results are normal, and if these are confirmed by a normal glycohemoglobin measurement, you are to be congratulated; you have a successful diabetes regimen!

If you are accurately following your doctor's advice and have poor control or other problems, your treatment program may need adjusting. There are many options. First, examine the basic program of diet and exercise, and make sure those are indeed correct. If oral agents fail despite these measures, your doctor will probably recommend insulin. If, despite correct measurement, mixing, injection, rotation, and dose adjustment, your insulin regimen works unevenly throughout the day (with high sugars at some times and low or normal sugars at other times), a more complex insulin regimen may be required. Today, two injections of mixed insulin is a fairly standard regimen, and we often recommend three or four injections to approach optimal control. Some patients may profit from using an insulin pump, which may offer more stable blood glucose control during the night and a bit more flexibility in the timing of feedings. Remember that such pumps, although programmable to deliver very complex regimens of insulin, are unaware of your blood glucose, and must be adjusted to change the regimen when your monitoring indicates the need. Other patients, with lipodystrophy (local wasting of fat at injection sites), insulin allergy, or insulin resistance may need the newer


Week beginning Monday:_____(Date)

DAY OF WEEK	Type of Action	INSULIN INJECTIONS: Insulin* Code	UNITS GIVEN: Morn	Aft	Eve	Night	MONITORING: BLOOD AND URINE: Tst	BREAKFAST Before	BREAKFAST After	LUNCH Before	LUNCH After	DINNER Before	DINNER After	Bed Time	Over Night	BG = Blood Glucose US = Urine Sugar UK = Urine Ketones NOTES:
MON	Short Acting						BG									
	Longer Acting						US									
	SUPP						UK									
TUES	Short Acting						BG									
	Longer Acting						US									
	SUPP						UK									
WED	Short Acting						BG									
	Longer Acting						US									
	SUPP						UK									
THURS	Short Acting						BG									
	Longer Acting						US									
	SUPP						UK									
FRI	Short Acting						BG									
	Longer Acting						US									
	SUPP						UK									
SAT	Short Acting						BG									
	Longer Acting						US									
	SUPP						UK									
SUN	Short Acting						BG									
	Longer Acting						US									
	SUPP						UK									

*The Code letter appears on your insulin package

Figure 5. The Squibb-Novo *Self-Monitoring Diary* is designed for those who use multiple insulin doses. Supplements are recorded separately to reduce the risk of accidental inclusion in the basal dose for the following day. As many as eight monitoring times during the day may be used without impairing the ability to compare one day with another. This log is available through physicians, some pharmacies, and the Squibb-Novo company.

highly purified animal or human insulins. As prices of these insulins fall, we may recommend them routinely for patients beginning insulin therapy, or even for all patients requiring insulin.

Summary

I have reviewed for you what I call *Stepped Care* for diabetes mellitus. This simply means beginning with basics and doing, step by step, what is necessary to achieve the goal level of control agreed on by doctor and patient. Some of you will require many more of these steps than others. Managing one's diabetes is a challenge; there is a lot to deal with. Now, fortunately, we have more ways than ever of attacking the problems diabetes presents. Join in my optimism that diabetes management will continue to become more effective and may someday even be easier!

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Psoriasis

Claude S. Burton, M.D., Peter W. Heald, M.D., and J. Lamar Callaway, M.D.

Thanks to Madison Avenue, we ore all fomiliar with the "heartbreak of psariasis." For 1-2% of Americans this nancantagious skin disease is more thon familiar and varies in presentatian from a minor cosmetic nuisonce to a disabling and rorely fatal illness. There is neither a cure nor o universolly successful treatment. By careful selectian from o great number of useful therapies (and some trial and errar), psoriasis can be satisfactorily controlled in virtually every case. Many af the medicotians we discuss are avoiloble withaut prescriptian and milder cases moy respand to self-treatment. When self-treatment fails, ar when the disease warsens, prafessional help is essential.

Whether yau pursue self-treatment ar a prafessianally guided appraach, aur limited knowledge af this disease will help yau manage the disease. Psoriasis is a disease influenced by genetic ond enviranmental factors. Many but nat all patients have a family history of the disease and many but nat all patients can relate the onset af their psoriasis to a strep throat, virol infectian, ar trauma ta the skin such as multiple wasp stings, sunburn, etc. Alcahal, certain drugs (Lithium, Inderal, ather beta-blockers), and emotionol stress are comman flare factars and shauld be avaided by all peaple with psariasis.

In skin affected by psariasis the epidermis or outer layer proliferates very fost. Whereas narmal skin campletes a growth phase raughly every 20 days, psariatic skin completes this pracess every 24-48 haurs. All of the therapies of psariasis are aimed ot slowing this growth. Psariatic skin is red due to the increase in blaad flow in the region ond scaly due to the ropidly accumulating epidermis. These red spots with silver scole an their surface are unsightly and aften itch intensely. If large surfoces are offected, fluid and nutrient lass may be significant ond the increased blaod flow through the skin may stroin the heart. Any or all of the skin may be involved. Elbows, knees, and ather sites of frictian are camman sites of invalvement. The scalp is anather common spot and many patients with psoriasis are seen in the office far intractable "dandruff." Arthritis is often seen in psariasis patients, indicating the possible systemic nature af this disease.

The name "psariosis" comes from the Greek ward for "itch." Psariasis antedates the Greeks, hawever, and apparently has been with us at least since man began to write. Early authars grouped this canditian with leprosy, adding to the misery af cauntless individuals with psoriosis. The shame and emborrassment assaciated with psariasis cantinues ta be a majar problem far anyone with the disease. Iranically, this embarrassment prevents many psariasis sufferers from enjaying the dramatic effect of sunlight on this diseose.

Sunlight is the cheapest of the available therapies. If the oreas af invalvement are expased ta the sun, a complete remission of the disease may accur after several weeks or manths af treatment. Since psoriasis aften involves parts of the bady considered private, and since many patients are too embarrossed by their appearance ta sunbathe, artificial sunlight in the farm of an ultravialet light cabinet or o partable sunlamp is o useful alternative to naturol sunlight. These artificiol sources have the advontage af year-raund, weather-independent avoilobility. Ultravialet light is not withaut hazard: premoture aging af the skin and the risk af skin cancer are causes far concern. A sunburn, which will flore psoriasis in many cases, is a threot with both natural and artificial ultraviolet light. Carefully graduated exposures are recammended. A number of spos around the world are dedicated to this climatic therapy. One such spo locoted on the Dead Sea has reported a response rote of 96%.

Oral dases of plant compounds knawn as psoralens markedly potentiate the effects of ultraviolet light. These agents are taken by mauth two hours prior to light expasure in a special cabinet producing light in the ultrovialet A range af the light spectrum. Ultraviolet A light tronsforms the circulating psoralen inta o malecule that is toxic to the rapidly dividing psoriatic epidermis. Thaugh effective in over 90% of patients, the therapy is nat far everybady. In additian ta the hazards af ultravialet light, there is o risk of early cataract farmation. Patients are required to wear filtering glosses on the day af treatment ta prevent activatian of the ingested psoralen as it circulates thraugh the eye. PUVA (Psoralen + UltraVialet A) is expensive and often inconvenient due ta distant treatment facilities and the time required far therapy and necessary precautions.

Topical steroids relieve the itching but they are expensive, messy, and associated with undesirable thinning af the skin, rapid and exaggerated relapse, and in same cases systemic absorption. Still, tapical steroids are useful in breaking the "itch/scrotch"

From the Department of Medicine, Duke University Medical Center, Durham 27710.

cycle that may worsen psoriasis and in suppressing symptoms during the early stages of the other therapies. Hydrocortisone cream is available over-the-counter, but the more potent topical steroids require prescription.

Crude coal tar in various topical formulations (many are available over-the-counter) slows the growth of psoriatic epidermis and relieves the itch for many patients. These remedies smell bad and are extremely messy for home use. Crude coal tar is a mix of some 10,000 compounds. One of these, anthralin, when extracted from tar, is much more effective than crude coal tar but requires a great deal of skill and time to use. Anthralin (prescription only) is applied to involved skin for varying amounts of time depending on patient tolerance. Anthralin slows the growth of the psoriatic epidermis and in time is capable of inducing a remission of the disease. Anthralin is extremely irritating to normal skin especially in body folds. It turns a dark brown on exposure to air and the staining of fabrics and in some instances bathroom appliances is permanent.

All of these topical and photo therapies are time-consuming and limited in usefulness by the associated mess. Though effective and reasonably safe, they do add to the nuisance associated with the disease. An alternative to these topical and photo treatments is oral agents. Of the many drugs under study methotrexate has emerged as the single most effective oral therapy for the treatment of psoriasis. Methotrexate, an antagonist of the vitamin folic acid, slows the growth of the psoriatic epidermis and is effective where other treatments have failed. Methotrexate is also very effective at controlling the arthritis associated with psoriasis. The use of methotrexate in low doses by mouth one day a week was pioneered at Duke by Dr. J. L. Callaway in the early 1950s. An informal poll of dermatologists suggests that this approach would be their choice for personal treatment if they had recalcitrant psoriasis. Although methotrexate is a marvelously simple therapy, skill in appropriate use of the drug is critical to its safe use. Laboratory studies (which add to the expense of this treatment) must be monitored until a steady response to the drug is established. Liver toxicity may occur in some patients particularly in association with a prior history of liver damage or in persons who drink moderate to heavy amounts of alcohol. The only way presently to monitor for this complication is by examination of needle biopsy specimens of the liver. Since liver biopsy is expensive and potentially dangerous, newer methods of monitoring for liver toxicity are being explored. Our group is studying the use of a new technique, nuclear magnetic resonance scanning (NMR for short), as an alternative to liver biopsy. NMR scanning does not require biopsy or needles of any sort, does not expose the patient to radiation, and may be accomplished as an outpatient at a fraction of the cost of liver biopsy.

With the advent of new techniques it is likely that psoriasis therapy will soon enter a new era of simple and effective therapies. Though the cause and cure elude us, we are in hot pursuit of both.



IT'S GETTING TOUGHER FOR NANCY RAY TO BE A MOTHER.

Nancy Ray has multiple sclerosis.

Every day it becomes harder for her to see. Harder for her to walk. Harder to do the things she wants to do for her family.

Four years ago, Nancy Ray was young and healthy. She was a mother with a four-year-old son, a teacher, a writer for educational TV.

Then, like about 200 young adults every week, she learned she had MS.

Multiple sclerosis destroys the myelin covering that surrounds nerve fibers in the brain and spinal cord. Messages to and from the brain get lost as they travel through the damaged areas. So your eyes, arms, legs don't do what you want them to do.

MS can be mild. Or it can be severe. Once you've got it, you've got it for life. Most days, Nancy Ray can get around with a walker. With a lot of time and effort, she can even prepare meals for her family. Some people with MS aren't that fortunate.

The National Multiple Sclerosis Society is helping people with MS live with MS. And funding research for a cure, all over the world. We can do it, but only with your help.

Please give generously. It's tough enough to be a mother without MS.

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JUST WHEN YOU'RE STARTING TO LIVE, MS CAN STRIKE.

Black Dermographism

Lester J. Fahrner, M.D.

• *An interesting and insignificant finding of black coloring on the skin after stroking it with good gold jewelry.*

CONDITIONS of no pathologic significance are often brought to our attention by our patients. These medical curiosities are sometimes a matter of concern to the patient. Probably just as often, the person considers the problem almost too inconsequential to mention to a doctor. We recently had the opportunity to see a patient with an unusual but insignificant finding.

At the end of a recent visit, a 36-year-old white woman mentioned that her children sometimes amused themselves by drawing on her skin with 14 and 18 carat gold jewelry. Her face or hands would be colored black wherever the gold was stroked. (See cover photos.) The pigment would slowly fade away over a few hours, or could be easily rubbed or washed off. "Cheap gold" or costume jewelry had no effect at all. She asked if we had heard of this before, and if we knew what caused it.

In the days after our interest was aroused by this patient, we saw a number of people with black coloration of the skin around their rings and on the fingers adjacent to those on which rings were worn. None of our other patients could easily draw on the face the way our original patient can.

We are all aware of the more common "problems" that jewelry can cause. Copper oxides and salts leached from inexpensive jewelry can stain the skin green. Moisture and soap trapped beneath rings and bracelets frequently leads to an irritant dermatitis. Allergic contact dermatitis due to nickel is commonly seen in areas under earrings, wristwatches, bracelets, etc.

Gold is quite inert chemically, both regarding oxidation and ionization. It is also soft, malleable, and easily polished to a fine sheen. These properties have contributed to its place as a most desirable precious metal. It was hard to imagine how gold caused our patient's dark lines. A glance at the dermatologic literature led to an appreciation of the phenomenon of black dermographism.

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Black dermographism was first reported in 1925 in the Russian literature. The nature of the condition was debated over the next five years in the German and Russian dermatologic journals. Various physical and chemical theories were put forth, some of which postulated that the patients were necessarily hypothyroid, neurotic, or hysterical. The initial patients were women who wore facial powders. Workers in some dusty occupations were later found to also exhibit black dermographism.

Urbach and Pillsbury[1] tested a number of finely powdered salts and commercially available face powders for their ability to induce black dermographism. When applied to the skin, coarse cloth, and filter paper, all the cosmetics and many of the metal salts made a satisfactory substrate for producing black lines when drawn on with metal objects made of silver, gold, copper, and many others. They proved with photospectrometric analysis that the black color is indeed the metal which has rubbed off onto the skin, paper, etc. All transition metals, when finely divided, appear black.

Optimal conditions are those that will lead to maximal friction: low lipid content, relative freedom from eccrine sweat, and intentional or incidental coating with a finely divided metal salt or oxide. Soft metals such as lead, silver, and fine gold "draw" more readily. Knowing this I thoroughly washed and dried my hands, dusted the dorsal surface of my hand with my wife's face powder, and rubbed black lines on my skin with an 18 carat gold ring. The color washed off easily.

If patients mention black coloration from their gold or silver jewelry, they may suspect "too much acid in the system," or that their loved ones are bestowing inexpensive gifts. You can explain that they are seeing a common, normal effect of metal rubbing against the skin.

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Insulin Can Make Diabetes Worse: The Smoldering Somogyi Effect

Linda M. Frazier, M.D. and Francis A. Neelon, M.D.

• *Nocturnal hypoglycemia can cause rebound hyperglycemia.*

DOCTORS have traditionally relied on measurement of urine glucose and fasting blood sugar to adjust insulin therapy; if the glucose is high, more insulin is prescribed. Paradoxically, this approach may sometimes result in even higher blood sugars. The following case illustrates how diabetic control may remain poor until the insulin dose is lowered.

A sixty-one-year-old man had a fifteen-year history of diabetes mellitus treated with insulin, 49 units (U) daily in two doses composed of a mixture of NPH and regular insulin. Fasting blood sugar ranged from 130 to 211 mg/dl (normal 75-110). His course was complicated by recurrent depression and during the nine months before admission he noted decreased appetite and difficulty falling asleep; he lost four pounds. He had occasional episodes of weakness, sweating, and palpitations, and was twice found wandering about his house with a glassy expression. One day he became confused while driving and crashed into a stopped truck. There was no loss of consciousness or seizure activity; his sensorium cleared spontaneously. He did not use alcohol.

On admission he was alert and oriented; physical exam was unremarkable. A mid-morning blood sugar was 297 mg/dl; creatinine was 1.0 mg/dl (normal 0.7-1.4) and thyroxine was 9.6 (normal 5.5-11.5). We suspected hypoglycemia precipitated by decreased food intake and used a Glucometer to monitor blood sugar in fingerstick blood samples at bedtime and at 3 a.m. We decreased insulin to 47 U daily in two doses of mixed NPH and regular insulin. The 3 a.m. blood sugar ranged from 44 to 80 mg/dl while afternoon and evening glucoses rose as high as 436 mg/dl. Fasting blood sugars (6:30 a.m.) were normal to slightly elevated, but episodes of hypoglycemia, especially at 2:00 or 3:00 a.m., were frequent, leading us to progressively decrease the total prescribed dose of insulin.

As the total daily insulin dose gradually decreased, peak serum glucose fell toward an acceptable range (figure 1). When hypoglycemia occurred at night, the blood sugar rose sharply the next day despite insulin administration (figure 2). When nighttime hypoglycemia was avoided, the blood sugar the next day was lower even though less insulin had been given (figure 3). When we reached seventy percent of

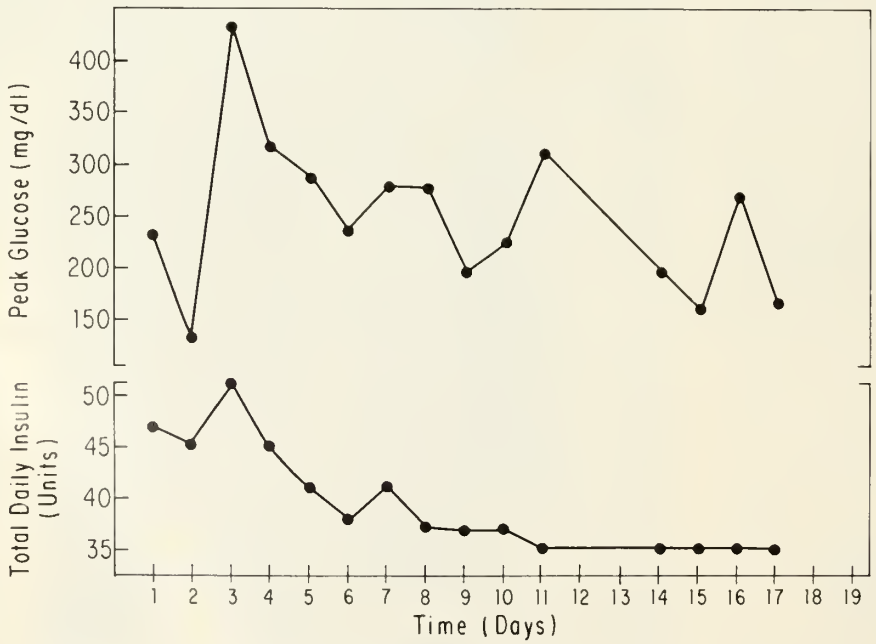


Figure 1. *Relationship of peak glucose each day and total daily insulin dose.*

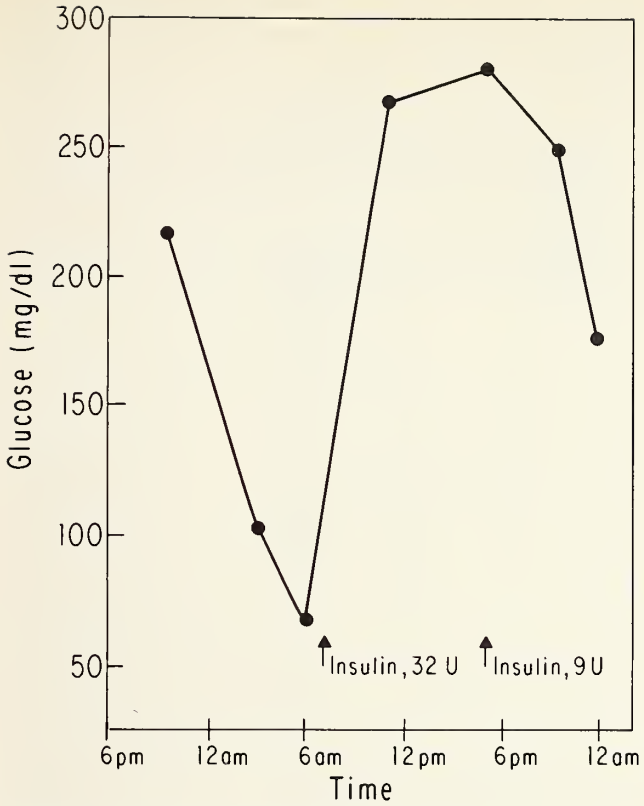


Figure 2. *Hypoglycemia causes glucose elevation despite substantial doses of insulin (hospital day 5).*

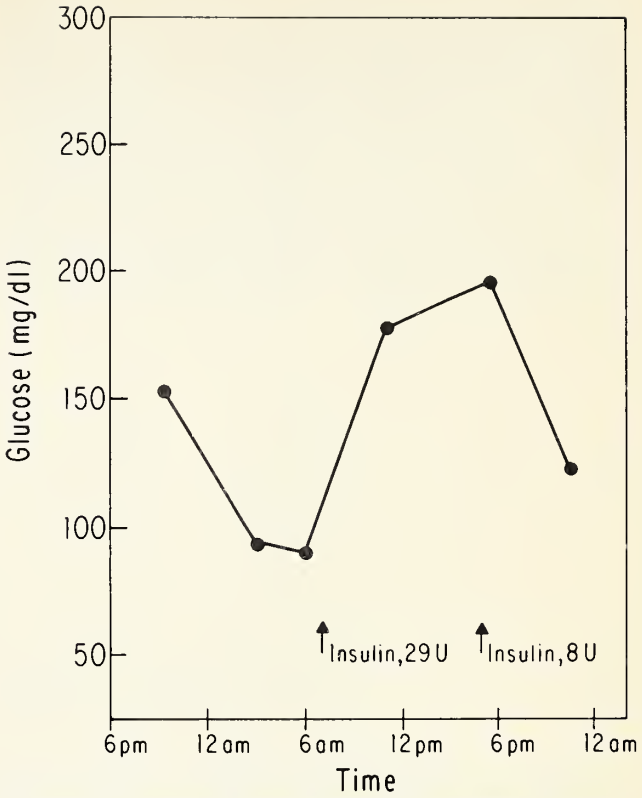


Figure 3. *Improved glucose control in the absence of hypoglycemia (hospital day 9). Afternoon blood sugar is lower than on day 5 (figure 2) despite a lower insulin dose.*

his previous insulin dose, hypoglycemia resolved and further adjustments were begun as an outpatient. The episodes of confusion stopped.

If we had not measured blood sugars at 3 a.m., we would have been tempted to increase his morning insulin in an attempt to control afternoon hyperglycemia. This would only have exacerbated nocturnal hypoglycemia and worsened diabetic control. Hypoglycemia causes several hormones to be released which have an "anti-insulin" effect including catecholamines, glucagon, growth hormone and glucocorticoids.[1] Catecholamines, glucagon and cortisol increase hepatic gluconeogenesis; catecholamines impede insulin release and peripheral glucose utilization. Hypoglycemia results in rebound hyperglycemia which will recur until hypoglycemia is eliminated. Keep in mind, however, that on the day *after* hypoglycemia, insulin needs are actually, but transiently, increased so no reduction in insulin dose should be made until the hyperglycemic rebound has passed.

The phenomenon of diabetes made worse by too much insulin was first observed by Michael Somogyi, a biochemist, in 1935.[2] At that time, mild hypoglycemia was felt to be harmless or perhaps even beneficial for diabetic patients. Insulin therapy was adjusted according to quantitative urine glucoses; when the urine contained large amounts of sugar, the insulin dose was rapidly increased. Dr. Somogyi studied several patients who were classified as "unmanageable" diabetics despite receiving insulin in doses of 95 to 150 U per day. He found that glycosuria followed a distinct pattern:

> . . . high glycosuric tides tended to follow days when the sugar in one or two urine fractions was close to zero, even though the spill for the entire day may not have been conspiciously low. . . . A fact that impressed us and was very significant was that glycosuria flared up with especial violence in the wake of pronounced hypoglycemic reactions.[2]

When Somogyi substantially reduced total insulin dosage, twenty-four hour urine glucose fell and fluctuated less from day to day.

The Somogyi effect should be suspected in compliant but poorly controlled diabetics even when they do not report frank hypoglycemic symptoms. Gale and Tattersall found nocturnal hypoglycemia in 22 of 39 poorly controlled diabetic patients;[3] six of these were asymptomatic. Patients with symptomatic hypoglycemia reported lassitude or depression, night sweats, undue difficulty in waking, early morning headaches, nocturnal seizures or vivid or disturbing dreams. Hypoglycemia at night does not mean that the routine morning "fasting blood sugar" will be low. In fact, Gale and Tattersall found only one patient to be hypoglycemic on routine blood sugar before breakfast. In the absence of symptoms, morning hypothermia or ketonuria without heavy glycosuria may be clues to unrecognized nocturnal hypoglycemia. In all cases, physicians need a high index of suspicion, especially in patients receiving more than 1.2 U insulin/kg/24 hours, although elderly patients become hypoglycemic at lower doses than this.

To diagnose the Somogyi effect before home glucose

monitoring became available, admission to the hospital was usually necessary for measurement of serum glucose around the clock. Several companies now market kits that allow patients to estimate blood glucose by the colorimetric change caused by a drop of blood placed on a strip of reagent-impregnated paper. Machines such as the Glucometer use this principle to provide a precise digital read-out of blood sugar. These instruments are easy to use, are becoming less expensive, and are sometimes partially reimbursable by insurance. They give patients with diabetes a measure of control over their condition that Dr. Somogyi would have envied.

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LEARNING WITHOUT WORDS

New Wine in Old Bottles

Francis A. Neelon, M.D.

• *A change in the formulation of Synthroid tablets may lead to inadvertent overdosage*

OCCASIONALLY drug manufacturers, in an attempt to improve their products, do an unwitting disservice to the patients who take those drugs. A recent change in the formulation of Synthroid (sodium levothyroxine) is an example of this as illustrated by the following case:

A thirty-five-year-old woman had had a thyroidectomy several years previously. She had a history of radiation treatment in childhood and the discovery of a goiter properly resulted in a recommendation for surgical removal of the thyroid. A microscopic papillary thyroid carcinoma was found although the clinically evident goiter had been due to Hashimoto's thyroiditis. There was no evidence of metastasis and the only treatment indicated was suppression of thyroid function with oral thyroxine.

For the past four years she has been on a constant dose of Synthroid (0.175 mg/day), a dose that has successfully suppressed thyroid stimulating hormone (TSH). After correction for thyroxine binding globulin concentration, serum thyroxine (T_4) had been slightly higher than the normal range, but serum triiodothyronine (T_3) had been within the normal range and the patient asymptomatic until last year when she experienced unexplained weight loss. Measurement of serum thyroid hormones showed a dramatic increase in T_4 and a T_3 value clearly above normal (figure 1). She had made no change in the prescribed Synthroid dosage and had faithfully taken the tablets as directed.

The explanation for this unanticipated result is contained in a letter to me from Dr. David L. Horwitz, Medical Director of Flint Laboratories in which Dr. Horwitz explains that Flint has indeed changed the formulation of Synthroid tablets and now uses a radioimmune assay to standardize the tablet size. The new procedure provides a more accurate dose and, in itself, is laudable. What is unfortunate is that the new tablets contain more thyroxine than the old (Dr. Horwitz thinks the change should not be clinically significant). Dr. Horwitz to the contrary notwithstanding, some patients (especially those maintained purposefully at the limit of tolerance) may become thyrotoxic

From the Department of Medicine, Duke University Medical Center, Durham 27710.

as I believe my patient has. Apparently other physicians have experienced problems similar to mine, because a recent issue of the *Medical Letter* (Volume 26, Page 41, 1984) cautions us to be alert to potential thyroxine overdosage in patients on Synthroid. Patients taking Synthroid should have their serum thyroid hormone concentrations checked and the prescribed dose changed if indicated. We also may have to recalculate the old rule of thumb for thyroxine replacement dosage (0.001 mg/lb body weight).

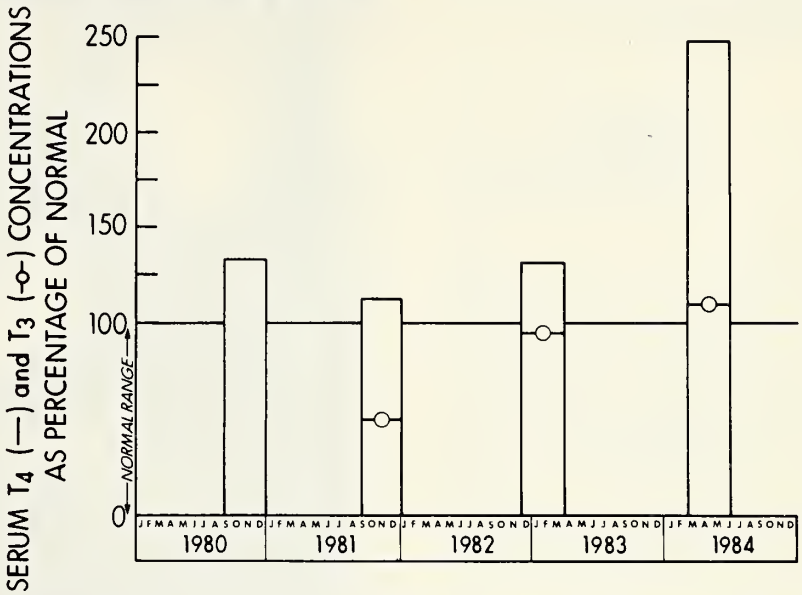


Figure 1. *Serum thyroxine (T_4) and triiodothyronine (T_3) concentrations, corrected for protein binding and expressed as percent of normal range, in a young woman maintained on a constant prescribed dose of Synthroid. In 1982 the manufacturer reformulated the tablets and those now reaching the marketplace contain more thyroxine than previously.*

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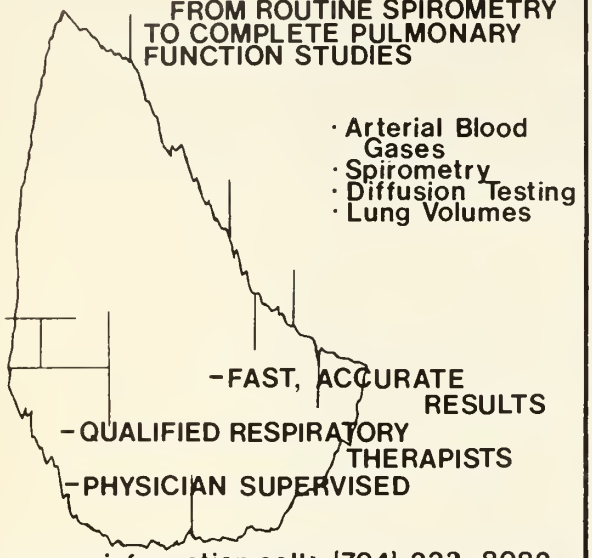
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From Grandma to Galen: Boric Acid Poisoning

Ronald B. Mack, M.D.

I believe that the spirit of Galen still lives!! Where, you ask? Why in the DNA of the world's grandmothers and great-grandmothers, of course. Galen of Pergamum, who lived from 130 A.D. to 201 A.D., was probably the second most famous of the ancient Greek physicians; Hippocrates is clearly the Oscar winner here.

Galen's major theory, which was primarily an elaboration of the works of Hippocrates and Aristotle, proposed that the human body was composed of four vital elements: *fire, air, earth* and *water*. These components made up the four major humors of the body: *blood, phlegm, black bile* and *yellow bile* (if you are reading this while you are eating, I apologize). Each of the humors had very definite qualities: *blood* was considered moist and warm, *phlegm* was moist and cool, *yellow bile* was warm and dry, and *black bile* was cold and dry.

The deficit or excess of a humor or humors was thought to determine health and temperament, e.g., blood = sanguine (cheerful, optimistic); phlegm = not easily excited, "cool"; yellow bile = choleric, irascible; and black bile = melancholy. Thus, the underlying cause of disease was viewed as a morbid state of the humors which were considered to be impure or in excess or in deficit or displaced. The treatment for a given disease depended on the state of the humors. If a humor or humors were excessive the patient was treated by depletion via bleeding, purging, sweating, etc. If the humor or humors were deficient the patient could be helped by attempting to restore the deficit by diet or medications. Galen classified drugs, accordingly, into groups that possessed one or more of the qualities of warmth, dryness, coldness, wetness. These drugs could be applied whenever a deficiency or excess of one or more humors mandated a counter action.

The teachings of Galen remained unchallenged until the time of Paracelsus in the 16th Century. In Colonial times in this country and well into the early 20th Century, Galenism was still quite popular. I believe the teachings of Galen still persist today in many segments of our population. The only way you are going to determine which of your patients are using these methods is to ask questions of them unless they volunteer the information without prodding (rare in my experience). It is most often a grandmother or great-grandmother who advises the younger members of the family to try a remedy that has "always worked before." It is a fair statement, I believe, that most people in this country do something to try to alleviate their symptoms before seeking professional medical aid. Some of the treatments they utilize would make Galen very proud indeed.

One of my most unfavorite medications is *boric acid*. Yes, it is still quite available and in the recent past we have had several calls concerning boric acid ingestion. Often the use of this terrible stuff has been recommended by grandma. (I apologize for seeming to be harsh on grandmothers. I love them!! I go to bed with one every night.)

Poisonings due to borates are not as common as they used to be, thank goodness, but occasionally cause problems both for the victims and their medical caretakers. These chemicals exist in both alkaline and acid forms. Sodium borate (AKA borax) is used as an antiseptic and a cleansing agent. The perborate form is used as a mouth wash. Boric acid was first used as an antiseptic by Joseph Lister in 1875. It is typically prepared by mixing sulfuric acid with sodium borate. This chemical is still used as an antiseptic and as an agent to make talcum powder flow more readily. Those of us old enough to remember can still recall using a boric acid solution to "wash our eyes" when we had "pink eye." (We used a device called an eye cup. I forgive you mother if you are reading this!) Boric acid solutions were also used as wet dressing for patients with thermal burns, diaper rash, skin ulcers and surgical wounds. This chemical was available in nurseries where it was responsible for many deaths because it was inadvertently used in infant formula preparation (because it resembles sugar, etc.). Nursing mothers were advised to wash their nipples with a boric acid solution before breast feeding. It is alleged that in the past it was used in the treatment of epilepsy.

Boric acid is not a good antiseptic as it is only mildly bacteriostatic. It probably is not good for anything. It is a wonder that it still is available to the unwary consumer. In my opinion it should be removed forever. Many of my patients use urine as a medicine, e.g., for tinea capitis, ear pain, oral candidiasis and contact dermatitis; it is probably safer than boric acid and just as much an anachronism. You can purchase this acid in powder or liquid form. Borates are easily absorbed from abraded or diseased skin, mucous membranes, and the GI tract. Many cases of poisoning in the past resulted from percutaneous absorption of the boric acid in the treatment of diaper rash.

The pathophysiology of boric acid poisoning involves the GI tract, CNS, skin, liver and kidneys. The kidneys are probably the most seriously affected of all the organs involved. Boric acid is said to be toxic to all cells but the

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mechanism of toxicity is unknown. The fatal dose is thought to be about 5-6 grams in an infant and 20 grams in an adult; it is fatal at about 0.1-0.5 gram per kilogram according to some authorities. In acute boric acid poisoning the clinical features can be quite frightening but of course non-specific. Early on, the *vomiting* and *diarrhea* of blood get your attention as well as the often severe colicky abdominal pain. Initially the effect on the CNS results in malaise, lethargy, restlessness, headache, tremors, and even *seizures*. In more severe cases *coma* ensues. *Fever* and *tachypnea* are quite common with increasing respiratory difficulties leading to arrest. The injury to the kidney is usually a renal tubular necrosis manifested by oliguria or anuria, and albuminuria. Jaundice is not common but is a possibility.

In my opinion, the most interesting toxic event in boric acid poisoning is the dermatological sequellae. The skin becomes quite erythematous with vesicles or papules appearing on the hands and ultimately becoming generalized. This results in what is referred to as the "boiled lobster" appearance (I don't care, I'm not going to give up eating lobster). The skin lesions advance to bullae formation followed by desquamation and sloughing. This is indeed the classic picture of boric acid poisoning and its presence should alert you to the possibility of this diagnosis. The skin lesions are not pathognomonic, of course, and do resemble scarlet fever or toxic epidermal necrolysis.

The diagnosis is usually a clinical effort; laboratory confirmation is not easy to obtain. Blood samples from victims of suspected boric acid poisoning can be analyzed without charge by the U.S. Borax and Chemical Corporation;[1] 10 ml of clotted blood (without an anticoagulant) should be sent via air-mail to Russell S. Fischer, M.D., Chief Medical Examiner, State of Maryland, 111 Penn Street, Baltimore, Maryland 21201.[2] Send the sample in a polyethylene bottle with a case summary. The company advises you to take an initial blood sample as soon as possible after the ingestion, another 24 hours post ingestion, and repeated samples as needed to determine a trend. Dr. Fischer is the Medical Consultant for the U.S. Borax and Chemical Corporation.

A rapid *qualitative test* requires one drop of the patient's urine acidified with HCl and applied to tumeric paper. This paper turns brownish-red if boric acid is present.

The urine often has red blood cells, protein, and epithelial casts in boric acid poisoning. Urine function and liver function tests should be monitored.

The treatment is less than thrilling; of course there is no antidote. Anything you do for the patient is usually only supportative. In ingestions that have occurred fairly recently, gastric emptying followed by activated charcoal is probably of some value. Dr. Fischer suggests the administration of glucose either orally as in "sweetened drinks" or by IV if the patient's condition warrants. He also suggests frequent monitoring of the patient's urine for rbc's.[3] Seizures can be controlled with diazepam. Needless to say, the maintenance of fluid and electrolyte balance is clinical here. Fortunately for all of us, boric acid lends itself to removal by dialysis, either peritoneal or extacorporeal. It is difficult to know when dialysis is indicated in these cases; blood levels are probably of no help here (even if you could get the results quickly enough); clinical judgment is the name of the game.

Maybe Galen wasn't such a bad guy after all. Plenty of people still practice his principles, e.g., many of our patients routinely take laxatives or give them to their children (whether they need them or not) to remove the "poisons or waste." In many Eastern European countries "cupping" is still in vogue. How many of your patients use chest rubs such as Vicks or use a mustard plaster on the chest? The most ubiquitous home remedy in our clinic in my experience involves the use of onions as a poultice, in the shoes or socks, in a hat, as a necklace, under the bed, as a drink, etc. Why I don't know, but Hippocrates spoke well of onions. Anyone who uses them medically should probably not be allowed to enter the 21st Century. Come to think of it, boric acid should not have been allowed to enter the 20th Century.

Let us not be so smug. Galen lives on in us as well, lest we forget "bleeding" via phlebotomy, dialysis, hemoperfusion, and plasmaphoresis and "purging" via ipecac and saline cathartics. (I love it!!)

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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocuranine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

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Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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EDITORIAL

Changing Perceptions of the End-Stage Renal Disease Program

William B. Blythe, M.D.

DR. Robert Gutman's article "Renal Dialysis for Kidney Failure in North Carolina: History, Practice, and Lessons"[1] in this issue of the *Journal* should be read and carefully contemplated not only by nephrologists but by **all** physicians. Contained therein is an account of the development of a life-prolonging biomedical technique, dialysis and, more importantly, an account of how our society has responded to its development. The technique and the reaction to it have become interwoven into a federally administered endeavor known as the End-Stage Renal Disease Program.

Dr. Gutman's paper *and* the End-Stage Renal Disease Program as it now exists raise important questions, some of which may be answerable now and some of which have more elusive answers, but all of which are sober and sobering. Furthermore, not only the answers but even the selection of the critical questions are to a large extent determined by one's profoundly held view of the nature of government, economics, and — ultimately — the nature of man.

Thus, as Dr. Gutman suggests, the lessons to be learned from the blemishes and warts as well as from the comeliness of the End-Stage Renal Disease Program may be, as is the perception of beauty, determined mostly by the outlook of the beholder.

I have been involved in planning for dialysis in North Carolina from the start some two decades ago. It is telling that those of us who have been involved that long have seen the cause for anguish change emphatically through the years. Early on it was the sad fact that dialysis was available to only a fraction of those who needed it. Lately it appears to derive from a perception in many quarters that 1) dialysis is not only available to all who need it, but is being employed in many cases where it may be of little help and 2) the cost of the End-Stage Renal Disease Program is either more than we can afford or more than it should be.

Why have we come to this position? First, what about the difference between the characteristics of patients who were selected for dialysis in the mid-sixties and those who are being selected for dialysis in the mid-eighties? As Dr. Gutman points out, patients who were selected for dialysis in the days of limited funding were younger and relatively free of complicating illness. This does not mean, it should be remembered, that older patients with complicating illness such as diabetes mellitus and hypertensive cardiovascular disease were not dying from end-stage renal disease. It does mean, in my judgment, that reality, in regards to the distribution of renal disease and the demographic characteristics of patients suffering therefrom, was not properly perceived by many responsible people.

In 1972, with passage of federal legislation that virtually eliminated money as a factor in selection of patients, reality began to be appreciated. It became clear in North Carolina that most of our patients had end-stage renal disease as a consequence of hypertension or diabetes mellitus and that most were older than we had thought. The medical decisions as to who was acceptable for dialysis became more difficult. Medical criteria therefore understandably became more liberal. I am certain that pitifully few — if any — patients have been accepted by nephrologists in North Carolina solely for financial gain; rather their dialysis rolls have been increased by the sicker and older because they had been there all along but now were clearly evident.

Furthermore, as one would reasonably predict, as the sicker, older and less sophisticated became an increasing percentage of the dialysis population, the percentage returning to gainful employment or acceptable rehabilitation decreased. It must be made clear, in addition, that this has not been solely a function of the degree of medical rehabilitation. Government regulations concerning disability, employer attitudes, and time away from work because of dialysis as well as other factors have played a major role. Thus, until we know considerably more about all these determinants, it is unreasonable to damn the End-Stage Renal Disease Program on this score. Drs. Gutman, Stead and Robinson[2] have made a major contribution in this regard and have set the stage for further dissection of the problems. It is imperative that we find out exactly what the situation is.

Now, what about the cost of the program? It *is* expensive. The cost of the End-Stage Renal Disease Program in 1984 will approximate 3 billion dollars. The increase in cost over the past decade has not, in general, resulted from an exorbitant rise in expense per patient, as Dr. Gutman reminds us, but rather from the tremendous increase in the number of patients who are in chronic dialysis programs.

Nevertheless, to my knowledge, no supplier of dialysis equipment, no corporation that has built and run dialysis units, no hospital and no nephrologist who operates a dialysis unit and/or cares for patients in dialysis programs has been close to financial exigency because of involvement in the program. Thus, I suspect, with a high degree of certainty, that there is still financial fat in many aspects of the program that can be safely cut away from the critical lean. This has to be done! But even if this were accom-

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plished in ideal fashion, the program would still be quite expensive.

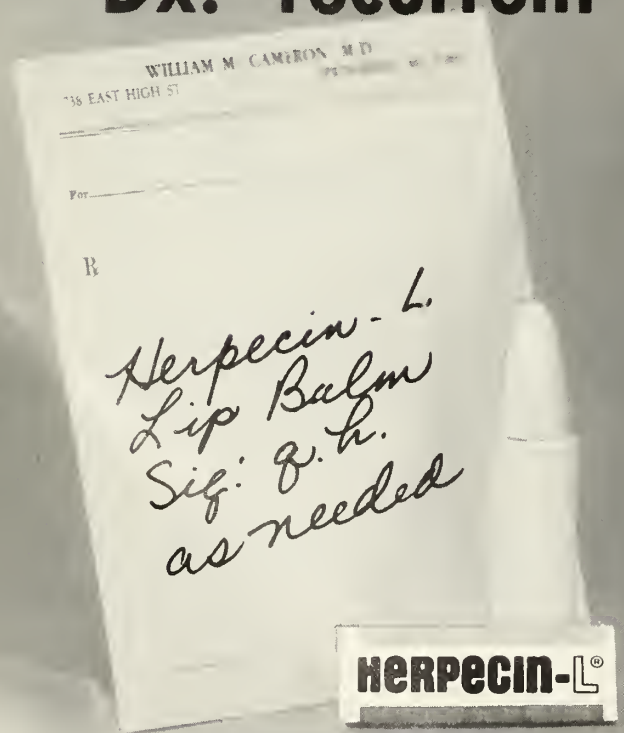
And then, in my judgment, the question becomes: How expensive is dialysis in relation to other things that government — and hence, society — undertakes? For example: public schools, aircraft carriers, super highways, military defense in outer space, education for physicians, bureaucracy, national parks, military aid to dictatorships, and on and on. I believe that we can afford it.

Finally, we must not forget that chronic dialysis is only an interim solution. Renal transplantation, all would agree, is the penultimate answer, and prevention of renal disease the ultimate one.

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Human Experimentation: The Ethical Dilemma

John B. Graham, M.D.

THE most succinct definition of ethics I ever heard was at a meeting of a pathology society, when in his presidential address, the president defined ethics and morals for the assembled pathologists this way: "When I hear you discussing ethics and morals, the definitions seem very simple. Ethics has to do with money, and morals has to do with sex."

A more enlightening if less humorous experience came during temporary service on the ethics committee of the American Heart Association. One of my colleagues in Chapel Hill had served on this committee for a number of years and wished to be relieved. He suggested that I be considered as his replacement, and arranged for me to be invited to Dallas for vetting, where I was asked to discuss the relation of genetic factors to heart disease. I listened to the discussion, mostly between doctors, with mystification for two days, then asked what was to me a simple question, but it shook them. I do not know whether they were shaken because of my ignorance or my naivete, but no one answered the question and I was not invited to return.* The question I asked was: "What should be the basis of medical ethics in a pluralistic society?" The lack of response surprised me, because this question has puzzled me for so many years. I suppose I should not have been surprised subsequently when I observed that theorizing about medical ethics had been taken away from physicians by lawyers and philosophers. My experience suggests that even a carefully selected group of doctors is unable to deal very effectively with such complex matters. Perhaps this reflects the shift during recent years from a classical to a technological concentration in premedical education.

Nevertheless, I asked a crucial question in Dallas. Let me explain. I am a Southerner, born and reared in the Bible Belt at a time when North Carolina was a very segregated society. But I have had the good fortune to travel widely, particularly during WW II as a soldier and between 1965-75 when I was active in the international population movement. I have seen many cultures and religions and have observed that theological beliefs lead to ethical outcomes that are widely variant. Cultures exist which either condone or condemn the same acts, e.g., homicide, contraception, abortion and infanticide. I saw a TV feature on family planning in mainland China recently which made me wonder whether infanticide involving babies who are abnormal at birth may not become NORMATIVE there. Their new policy of only one child per couple puts enormous pressure on parents for perfect babies. If practiced, selective infanticide would reduce the frequency of certain congenital defects, and might result in a marked change in the sex ratio of the next generation in the direction of a favored sex. Chinese have historically preferred males. Furthermore, the elimination of the children who are obviously abnormal at birth would reduce the frequency of many congenital anomalies and be a powerful selective force acting to reduce the frequency of the genes responsible for autosomal dominant traits. There would be little change in the frequency of recessive genes, but the frequency of recessive traits would probably decrease because of a reduction in in-breeding. There would be little effect on traits that do not become manifest until later in life, high intellect for example. Whatever its consequences, the one child policy is an obvious solution to the dilemma that faces the Chinese because of their enormous population, and this is the context in which we must now do our thinking. We must try to re-think our positions on various ethical questions before we are forced like the Chinese to consider tremendous changes.

My first attempt to establish a personal position on medical ethics was simple and practical, and I suspect that most physicians have done something similar. I fell back on the ethical values I picked up during childhood, e.g., the Golden Rule and the story of the Good Samaritan, modified in sundry utilitarian ways. I do not pretend that I have found a much better philosophy in recent years, even though I have continued to struggle with the philosophical contradictions and inconsistencies that have bothered me since childhood. What I mean by the latter comment is that I decided to become a physician largely because it seemed to a teenager to be a solution to the puzzling problem of reconciling ethical values and life in the real world. I was unable to see how to simultaneously practice the Golden Rule and succeed in business.

It has been a long time since the simple statements of the Hippocratic oath have been very useful to medical practitioners or to thinkers about medical ethics. Medical ethical values constantly change because the technology and content of medicine are rapidly evolving. Technological change has been so fast recently that institutes, specialty journals, and national meetings have sprung up which deal solely with problems of medical ethics. Let me give three examples.

1) The Hastings Center is a voluntary agency located north of New York City which was organized by a former Catholic theologian. It operates on contributions and publishes an excellent journal. I have been a subscriber since 1973, and I find articles of interest in almost every issue.

* My interaction with the AHA was not a complete disaster. I converted my presentation into a paper later published in *Perspectives in Biology and Medicine* with the title "Ethical and social issues posed by genetic studies of cardiovascular disease" (20:260, 1977).

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The Center has been particularly concerned recently with the abortion issue, the application of genetic engineering to humans, the problems of the homosexual, the AIDS syndrome, how to manage badly disabled infants, and the elderly.

2) The Kennedy family has endowed an institute at Georgetown University devoted to studies of "bioethics." The institute, now headed by Dr. Edmund Pellegrino, has published an encyclopedia which contains papers on almost every conceivable topic in biology and medicine which might cause ethical problems.[1] This approach to the subject has been analyzed and cogently criticized by two well-known medical anthropologists, Renee Fox and Judith Swazey.[2]

3) Recently I received a flyer advertising a national conference whose purpose was to implement in community hospitals the findings of the President's Commission For The Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. I seem to be invited to 4 or 5 similar meetings each year. The speakers are lawyers, philosophers, nurses, social workers and physicians. The keynote speech at this one was to be given by Morris Abram, a lawyer and former President of Brandeis University. He was also Chairman of the now defunct Commission. His topic, *mirabile dictu,* was "Ethics in a Pluralistic Society"! I am happy to see that he is attacking the problem which has interested me. I look forward to whatever answers he has found.*

Hippocrates's implied injunction relative to medical experimentation was very simple. He said, "Do no harm." Certainly no physician or ethical investigator wants to do harm. On the other hand, this was not a very useful guide, as physicians discovered well before our own day, and technological progress has made the problem considerably more difficult.

At the beginning of the century, American medicine, led by Dr. Benjamin Rush of Philadelphia, had developed what has been called a system of "heroic medical care." It was tough upper lip all the way! Surgeons operated without anesthesia, and it was regarded as character building to undergo an amputation without having the pain deadened. This type of medical care was being widely practiced when general anesthesia was discovered in mid-century. The use of inhalation anesthesia in its various forms and pain deadening drugs of the opium type were adopted very rapidly. The initial debate concerned the character destruction that might result from the use of pain deadening agents. Then it was discovered that ether and chloroform were toxic to the liver, and opiates could be addictive. The debate shifted to how to calculate the costs vs. the benefits of the abolition of pain. This is essentially where we are today. Every new therapeutic agent, operation, or device is carefully examined from the point of view of usefulness, as to whether it is better than another therapy, and whether its side effects are worse than the condition being treated.

Let us look more closely at the classical definition of the physician's role: restoring health, preserving life, and combatting suffering. What is he to do when the three are in conflict? What is to be done when relief of pain requires the giving of a dangerous drug; or when curing a disease requires radical and disfiguring surgery; or when life can be preserved only at a high cost in pain and anguish? Should a terminal cancer patient be given a potentially lethal dose of painkillers? Should heroic therapy be used to achieve a brief prolongation of life during a terminal illness? Everyone agrees that the duty to relieve suffering overrides the duty to prolong life. But is there a particular type of assessment that might provide answers to such ethical dilemmas?

This predicament led Joseph Fletcher and others to propose "situational ethics" as the solution about two decades ago. Situational ethics is the term that stands for the idea that each instance should be ethically judged on its own merits. This sounds like an excellent way to solve ethical problems. The difficulty is that it is extremely time consuming. It means that a physician can deal with only a few patients, because much of his time will be devoted to the systematic philosophical analysis that precedes the taking of action. In complex circumstances, the patient might expire before the doctor completes the analysis.*

What are the special ethical problems posed by human experimentation? To try to answer this, I shall turn to my ten year experience on NCMH's institutional review board (usually referred to nationally as an IRB), a group appointed by the Dean of Medicine and which actually bears the title: "Committee on Protection of the Rights of Human Subjects." I shall describe some aspects of the problems I observed and how we reacted. What we actually did was practice ethical calculus.

The committee consists of 14 to 20 persons, depending upon weather. It is widely representative of the medical center, and it includes 4 lay representatives from the community. A rotating cadre of students has been added recently. It meets monthly, and there are usually 10-20 items to be considered. It faces problems raised by the development of new drugs, new appliances, new diagnostic and surgical procedures, administration of novel types of radioisotopes, etc. I shall describe the evaluation of a new and untried drug from discovery until approval, because although this matter looks relatively straightforward, it is complex and controversial and raises all facets of our main question.

Before a new drug can be introduced into regular medical practice it must undergo an extensive screening procedure leading to approval by the Food and Drug Administration. The drug was probably synthesized in a chemical laboratory somewhere and has been found to have a therapeutic effect of some sort, probably by testing it on an animal. What must be understood is that every potential drug is also a potential poison. After a therapeutic effect has been discovered, the toxic side effects are examined in experimental animals by the manufacturer or his delegate. Ethical problems arise early, because there are those who

* Mr. Abram has been in the news lately in another context, having just been appointed chairman of the Commission on Civil Rights by President Reagan. You may have seen him on television locking horns with Dr. Mary Berry, a member of the recent Carter administration. One cannot help admiring Mr. Abram. I don't know whether to admire him more for tackling the issue of ethics in a pluralistic society or for taking on the formidable Dr. Berry.

* In recent years philosophers and/or theologians have been recruited to medical faculties, e.g., Joseph Fletcher at the University of Virginia and Larry Churchill at UNC. There is now an elective course in medical ethics at Chapel Hill.

doubt that animals should be used for these purposes. Yet there seem to be few ways to discover the therapeutic value of drugs except by observing their effects in animals. Notable exceptions are the drugs that are useful against bacteria and cancer. Their effectiveness can be partially evaluated in bacterial or cell cultures.* But how can we discover in cultures a drug that has an effect on consciousness or blood pressure? With important exceptions, there are few avenues other than animal testing that evaluate toxicity adequately. The exceptions are mutagenicity and carcinogenicity which can be tested for in cultures. But these are only two of the many toxic effects that concern us. Some drugs do not become toxic, for instance, until they have been transformed by exchange between the cells of the different organs within an animal. There is no way to establish cell cultures or sets of cell cultures, which simulate animals, even using computers! An intact animal whose metabolism is similar to man's provides the only entirely reliable test system. If non-human animal studies were to be abolished the development of new drugs would have to cease, unless we were willing to use humans in their stead. To believe that we should cease to make new drugs is an entirely respectable intellectual position. However, those who advocate continuing to develop new drugs, and also advocate abolition of toxicity studies in animals can profess this view ethically only under the following proviso: They must be willing to volunteer their own bodies.

When animal studies have shown that a drug is not too toxic, this must still be verified in humans. All new drugs must undergo what are called first and second phase human studies before they are approved by the FDA, since the metabolism of no other mammal is exactly like that of man.

In first phase human studies the proposed therapeutic dose of a drug must be shown to be essentially nontoxic in volunteer subjects. Many drugs that are not toxic in usual doses may be highly toxic in larger doses. Furthermore, a dose that is suitable for the average subject may constitute an overdose for subjects who are overly susceptible for genetic reasons. It is impossible to be absolutely certain that a drug is innocuous to everyone.

If the toxicity studies are successful, it is then necessary to study the effectiveness of the agent, phase two. Is it really better than a similar agent? If it is either clearly less toxic or clearly more effective, it will probably be widely adopted. At a teaching hospital, the members of the faculty are frequently involved in testing drugs for pharmaceutical companies, both in first and second phase studies. At almost every meeting, our local IRB considers one or more new drugs or new uses for older drugs.

In addition to new drugs, there are new appliances or procedures such as isotopic scanning, new forms of radiation therapy, cardiac catheterization, diagnosis of brain tumors by isotopes, use of nuclear magnetic resonance spectroscopy, etc. to be evaluated. Sometimes the requests come from members of the faculty who have developed appliances, but more often a manufacturer wants a faculty member to test the utility of a new device. The IRB must be certain that application of the new tool or procedure does not endanger the subjects in any way or impair their rights. It also asks whether the expected benefits might be obtained in a simpler or cheaper fashion. The committee always makes an estimate of the risk versus the benefit. It tries to judge whether the gain to the patient outweighs the risk. This question must be settled before the new apparatus can be ethically put into use in the hospital.

Another type of problem arises when a new diagnostic procedure is suggested. Someone thinks or discovers that a new procedure may provide clearer evidence for or against the diagnosis of some disease. But the procedure itself is dangerously invasive or unpleasant. For example, prenatal diagnosis can be carried out by studying bits of the placenta of pregnant women utilizing the methods of recombinant DNA technology. The risk is that obtaining the tissue may lead to a miscarriage. The question comes down to an estimate of the ratio between the danger of using the procedure and the benefit that might accrue from its use.

Why are such problems presented to an institutional review board? Where do they come from? It seems to me that the proposals originate from about five sources.

1) Young, energetic and enthusiastic faculty members who put forward new ideas about improved diagnosis or therapy that need testing. If they are correct this outcome will lead to publication and the authors will enhance their reputations. Most of the proposals come from this group.

2) Pharmaceutical firms or foundations whose products must be reviewed by a reliable group, such as the staff of a university hospital. They recruit faculty members as agents and expect the institution to provide the subjects. This is not a type of research that often brings high acclaim to faculty members, but it is very useful to society.

3) Federal agencies in the area, particularly the Environmental Protection Agency and the National Institute of Environmental Health Sciences. The staffs are studying the effects of toxic substances on humans, and they often wish to define the effects of, say, lead or carbon monoxide on the function of the heart or lungs. They usually propose well-designed experiments involving volunteer subjects. Some of their employees are also faculty members, and some of the agencies have established special facilities on the campus.

4) "Cooperative Cancer Protocols." The doctors who specialize in treating cancer, the oncologists of our country, have banded together, by specialties, to test the efficacy of various combinations of drugs on the treatment of various types of cancer. Their proposals are formulated at a central location, and then farmed out to the institutions belonging to a consortium. Our institution belongs to several such consortia.

5) Graduate students. They wish to do thesis research on human subjects, the research project being a requirement for the graduate degree. Of course the work is carried out under the direction of a responsible faculty member.

The members of the local IRB have seen many examples of these different types of requests. In each case, the committee has judged the proposal by criteria established earlier as necessary for ethical experimentation on humans. I wish to emphasize that a physician who tried to avoid the

* The original cancer drugs were discovered by studying their effects on animals that had cancer. More recently cultures of cancer cells have been devised for screening potential cancer drugs. Everyone agrees that any test tube method that accomplishes the same task as animal studies should be adopted.

sometimes tedious IRB process would be disciplined. An investigator must provide suitable answers to the following questions:

Will the subjects truly be volunteers?

Will "informed consent" be obtained from these volunteers?

Is the study sufficiently well organized that a clear-cut answer can be obtained?

Is this the testing of a new procedure or merely the testing of a substitute for an already established and satisfactory procedure?

Will the results obtained be held in confidence?

Is the result, if obtained, sufficiently important to justify doing the experiment?

These are stringent questions and investigators are compelled to answer them. If answers are not forthcoming, or are not satisfactory, approval is withheld. Problems may arise in the following areas.

Volunteers

Many proposals are carried out on normal subjects, e.g., the Phase I drug toxicity proposals. The investigator usually advertises for and pays volunteers for compliance. Volunteers are plentiful in the Triangle area.*

It is more difficult to obtain volunteers when the subjects are patients. If the experimenter proposes to test the efficacy of a new agent against a condition that is not life-threatening, affected persons are often quite willing to cooperate. They are sometimes eager to test new agents for relatively benign conditions, such as acne, for which present agents are far from perfect. They may well benefit from participation in the experiment.

But finding volunteers is more difficult when the disease is life-threatening. When patients understand that they have apparently intractable cancer they may volunteer. But they are less willing to volunteer if the outcome is more hopeful, unless there is evidence suggesting that the new therapy may be better than present therapy. It would be unethical for a physician to attempt to force cooperation with the testing of a new treatment by suggesting or implying that the current therapy might be withheld otherwise. Knowledge of such an occurrence would bring down on an investigator the full wrath of the committee.

Informed Consent

Each experimenter must prepare a special consent form for his project. This is supposed to explain to the subject, in layman's language, all the risks and benefits. Then being informed, the subject gives or withholds consent.

The consent forms are very often poorly prepared. They tend to be badly written, full of jargon and technical terms, and hard even for committee members to understand. The committee returns more proposals to investigators because of badly written consent forms than for any other reason. My feeling is that even when the consent forms look and sound good to committee members, they are often unintelligible to subjects. Many patients are of reduced physical or mental capacity, or are poorly literate. They often stand in awe of the investigator, tending to agree uncritically with his suggestions, and don't want to challenge him. He is their doctor! There is good empirical evidence that the degree of understanding by a subject is inversely related to the length of the consent form, and some of the forms are 2-3 single-spaced pages!

Informed consent is a special problem when the subjects are fetuses, infants, or the elderly. It is a real problem, for example, to be certain that one has obtained informed consent to study Alzheimer's disease (senile degeneration). How can anyone be certain that the patient has understood and that manipulation has not occurred?

Organization of the Project

It is usually easy for the committee to decide whether a proposal has been so organized that a clear answer can be obtained. When this is not the case, the proposal is returned to its originator. It is usually revised and returned, but a few are so poor that they never again see the light of day.

Improving an Older Therapy

Many proposals are not aimed at testing radically new therapies. Rather there is an attempt to obtain marginally better results from an accepted one. If acceptable by all other criteria, and there is no added risk, these proposals are usually approved.

Confidentiality

Many investigators propose to collect personal data on large numbers of subjects for statistical analysis. Our rule has been that the subject's name must be so coded that no possibly embarrassing information can fall into the wrong hands. This is particularly important when psychosocial information is being collected.

Importance of the Experiment

The committee is seldom unanimous about the importance of a suggested experiment. There is clearly a sort of "Heisenberg principle" operating, and it would seem that "importance," like beauty, lies in the eye of the beholder. But in the absence of strong objections, and all other criteria having been met satisfactorily, an experiment is usually approved on the ground that the committee is not infallible and could be wrong about its importance.

Conclusion

I found service on an IRB to be very interesting and informative. I learned what many of my colleagues were doing without expending much energy, and got to know a number of interesting younger people whom I would never have met otherwise. (This is, of course, the real justification for large committees.) I felt on a number of occasions that we had shielded subjects from unnecessary risks. In the main, however, the proposals were satisfactory and were approved. As sportswriters sometimes say about athletic programs, the review of human experimentation at NCMH

* Consideration of the ethics of experimentation on human subjects, volunteers and patients, is much more advanced in the USA than Europe and Japan. It is at present the subject of intense debate in both Britain and France.

now has tradition. The medical faculty know that the committee exists, know that it is critical, and know that it must be reckoned with. Badly prepared and/or inappropriate proposals are now very rare.

As for my own contribution, I decided early on to play the role of Hippocrates. I left detailed criticism of the consent forms to our lay members, and left detailed criticism of scientific validity to my better educated younger colleagues. I attempted merely to be certain that none of the proposals did any harm.

So what are the special ethical dilemmas of human experimentation? It is not that the issues differ in principle from ordinary issues of medical ethics. It is that the issues are so complex and the ramifications so obscure that it is sometimes impossible to unravel them in any sort of timely fashion. Yet the subjects, patients, cannot be set aside to await the ethical analysis. The technical questions and their ramifications are often beyond the comprehension of the lay members and even the scientists. Yet the IRB must function as a "situational ethicist" functions, making ethical judgments about experiments on humans on a case-by-case basis. Sometimes I felt certain that the ethical analysis and the conclusion were correct. Other times I felt that the ethical situation was unanalyzable. Yet a decision had to be made. It was on these occasions that I reached for Occam's razor and cast my vote, based upon my calculation of the probability that harm would result. Thus we see that examining the ethics of human experimentation merely provides another venue for agonizing, existential decision-making. This is what physicians have always been expected to do and is why, when they are true to their principles, they are so highly regarded.

References

1. Encyclopedia of Bioethics, 4 v, Reich, WT, ed, The Free Press, 1978, New York.
2. Fox, Renee C and Swazey, Judith, Medical morality is not bioethics — medical ethics in China and in the United States, Persp Biol Med 1984, 27:336-360.

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Inaugural Address

Linda P. Nance

AS I stand before you today, I think of the many invested hours of preparation that have brought me to this point. The travel that has taken me to your counties and districts has left me with treasured friendships and I feel that I know about many of your opportunities. It is, therefore, with a great sense of pride and honor that I step forward to serve as your president.

There have been many women who have given outstanding leadership to the North Carolina Medical Society Auxiliary, a beautiful string of pearls. These women have brought us to the position of importance which we hold today. The eighties have seen great growth and change in the professional quality of what we offer in leadership training, opportunities for personal growth, and one-on-one contact between state officers and county members.

The world is in a state of change, and the Medical Auxiliary has attempted to keep up with these changes. We are not just a Women's Auxiliary now, we have male members, and women's roles are different. We are attempting to address these changes with programs that will develop one's potential. The National Auxiliary has developed the Professional Skills Program to document seminars, workshops, and educational participation which can be applied in the business world or in building self confidence. In this way we promote ourselves, our skills, and our organization.

As an organization we can effect positive change in our communities. There are many opportunities for us as medical families to make a difference. We can make citizens aware that there are ways to cut medical costs by changing the way they live. Fewer than 40% of North Carolinians BUCKLE UP when they drive; there were 2,700 lung cancer deaths in 1983; 13% of the adults in North Carolina lead a sedentary lifestyle; and North Carolina exceeds the national average in the incidence of high blood pressure, diabetes, arthritis, and strokes. Does it sound too simple to say that all of this could change if people stopped smoking, used seatbelts, got more exercise, ate nutritiously, and did not drink and drive?

This is where we as Auxilians can make a difference. I hope you will arm yourselves with the facts and educate the members of your communities as to the ways in which they can improve the quality of their lives. Work with your county Medical Society to form a partnership to help promote a positive image for medicine.

Because at least 625,000 children in the United States are reported abused or neglected each year, the state's major focus for the 1984-1985 year will be Child Abuse and Neglect: Its Awareness and Prevention. Your Health Projects Chairmen will offer suggestions as to ways you might establish educational and support programs in your communities. The Legislation Chairman is keeping her finger on the pulse of the political scene for pending legislation pertaining to child abuse. Throughout the year she will keep you informed about this and other legislative issues facing medicine today. In September there will be workshops about automobile safety restraints, prenatal and postnatal care, and nutrition which will address the growing problem of anorexia nervosa and bulimia.

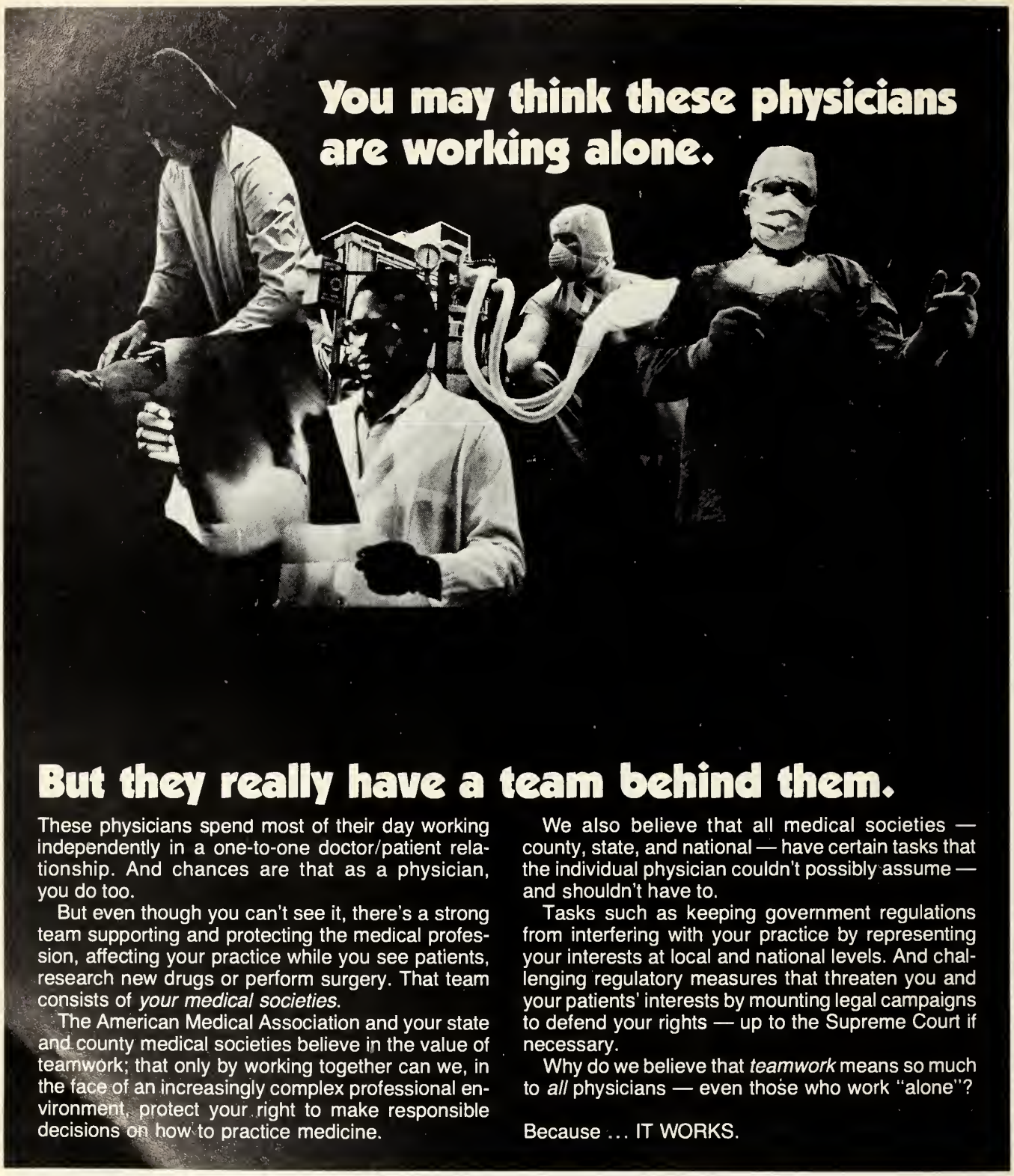
I have chosen as my theme, MAKE WAVES. I hope each of you here today will be inspired to return to your county to demonstrate our organization's concern with the public health of its citizens. Educate them about health-related issues with media spots, community programs, and by the example you set. From the programs that we will offer, you should find a project that will fit your Auxiliary, large or small. Continue to sponsor programs that are successful and still vital, but explore the needs in your community to see what you can do to expand your impact. You can make a difference!

Your officers are anxious to assist you in implementing programs, to help you meet your specific opportunities, or to be available when you need any advice. Please call on us.

Like the beautiful butterfly that emerges after the changes in its cycle of development, let us capitalize on what our predecessors have accomplished to make the mid eighties important years in our Auxiliary's history.

Shape Up For Life, MAKE WAVES in your communities. Let everyone with whom you come in contact know that you care about what happens to them. Make small waves or large ones when you implement programs and projects which you have found to be needed. By this time next year you can tell all Auxilians whether the song of the sea ends at the shore or in the hearts of those who listen to it

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IN STATE

June 17-22
Health Promotion — Wellness Institute
Place: Raleigh
Fee: $250
Credit: 30 hours
Info: NC Health Promotion, Wade AHEC, 3000 New Bern Avenue, Raleigh 27610. 919/755-8018

June 20
Suicide by Poisoning
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St., Sandord 27330. 919/774-4100, ext. 340

June 22-23
35th Annual Meeting and Scientific Sessions
Place: Durham
Info: NC Heart Association, Chapel Hill 27514

July 9-14
26th Annual Postgraduate Course/Morehead Symposium
Place: Atlantic Beach
Credit: 25 hours
Info: C. Easterling, Box 3108 Duke Hospital, Durham, 27710. 919/684-6878

July 13-14
34th Annual Blue Ridge Institute
Place: Black Mountain
Info: C. Scott Venable, American Lung Association of NC, 916 West Morgan Street, Raleigh 27611. 919/832-8326

July 18
Hospital Nutrition Update
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St., Sanford 27330, 919/774-4100, ext 394

July 19-21
Sixth Annual Mountain Meeting
Place: Asheville
Credit: 12 hours, Category I AMA
Fee: $150
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

July 30-August 3
Diagnostic Imaging
Place: Atlantic Beach
Fee: $400
Credit: 26 hours
Info: J. D. Wright, Box 3808, Duke Hospital, Durham 27710. 919/681-2711

August 4
Geriatric Education Day
Place: Raleigh
Credit: 4 hours
Info: NCAFP 919/781-6457

August 7
Malpractice Awareness — STAT
Place: Greensboro
Info: Wayne Parker. 919/828-9334

August 14
Malpractice Awareness — STAT
Place: Charlotte
Info: Wayne Parker. 919/828-9334

August 15
Electrolytes/Arterial Blood Gases/Fluid Balance
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St, Sanford 27330. 919/774-4100, ext 394

August 21
Malpractice Awareness — STAT
Place: Goldsboro
Info: Wayne Parker. 919/828-9334

August 24, 26
Summer Urology Conference
Place: Winston-Salem
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

OUT OF STATE

June 18-July 1
The Cancer Patient: Surgical Treatment and Rehabilitation
Place: Cruise Benice, Yugoslavia, Greece, Turkey, Russia
Info: C. Easterling, Box 3306 Duke Hospital, Durham 27710. 919/684-6485

June 18-22
New Horizons in Radiologic Imaging
Place: Charleston, SC
Credit: 20 hours, AMA Category I
Fee: $350
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103.

June 27-30
Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Credit: 15.5 hours Category 1 AMA
Fee: $350
Info: Dermatology, Box 2987 Duke Hospital, Durham 27710. 919/684-6728

July 2-7
Midsummer Family Practice Digest
Place: Myrtle Beach, SC
Credit: 30 hours
Info: NCAFP. 919/781-6467

July 26-28
6th Annual Pediatrics Primary Care Conference
Place: Virginia Beach, VA
Credit: 12 hours
Fee: $275
Info: S. Rosner, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

July 30-August 3

12th Annual Beach Workshop
Place: Myrtle Beach, SC
Credit: 20 hours AMA Category I
Fee: $225
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

August 12-17

Symposium on the Surgical Treatment of Cancer
Place: Orlando, FL
Credit: 20 hours Category I AMA
Info: C. Easterling, Box 3108 Duke Hospital, Durham 27710. 919/684-6878

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Letters to the Editor

Allergies

To the Editor:

On January 9, 1984 I saw an 18-year-old white woman whose complaint was swelling of the eyes and throat.

Her first encounter with this reaction was on August 20, 1983. Her boyfriend had been trimming walnut trees and then came to visit her. Fifteen minutes after exposure to the walnut sap on his body, her eyes began to itch and swell. They did not completely swell shut. Her symptoms lasted three to four hours.

Two days later he again visited her after trimming trees and again had the walnut sap on his arms and wrists. Fifteen minutes after he arrived, her eyes swelled completely shut, her face was puffy and she experienced difficulty in breathing. She described this as feeling like her throat was closing and a tightness in her chest. She was taken immediately to the emergency room where she was given an injection of epinephrine and 25 mg of benadryl. She was released after 1½ hours with benadryl to carry home. Her symptoms lasted three to four days.

Four months later, she came home from school and ate an apple. Thirty minutes later she ate an orange. Then ten minutes later she ate a tangerine and a peppermint patty. After 15 minutes her eyes again swelled completely shut and the same difficulty in breathing was experienced. She took 50 mg of benadryl but to no avail. She was taken again to the emergency room where she was started on an I.V. of Jelco and Dextrose. She was given an injection of epinephrine and an injection of benadryl 50 mg, along with an injection of Decadron. She was kept in the emergency room for 5 hours before being released. She was given benadryl 25 mg capsules and an Ana-Kit to be used if necessary.

The most interesting and most important fact about this history is that sap is a rosin and rosin cross reacts with balsam of peru. Balsam of peru can be found in the following: topical medications, cements, liquids in dentistry, Anusol suppositories, Rectocaine suppositories, Endacaine compound suppositories, Granulex, rectal Medicone suppositories and ointment, Wyanoids HC, Calmol 4, Melynor ointment, cosmetics, hair tonics, perfumes, flavoring industry, china painting, oil painting, and adhesive tape. Balsam of peru cross reacts with the following: benzoin, rosin, benzoic acid, benzyl alcohol, cinnamic acid, essential oils, orange peel, eugenol, cinnamon, and clove.

Such a patient should be especially cautious when preparing for dental work. She should be patch-tested before any dental work is performed; otherwise a severe reaction could occur.

Balsam of peru cross reacts in many foods such as orange peel, celery, cinnamon, and clove. This would explain her reaction after eating the orange and tangerine.

I gave the patient information on where rosin and balsam of peru are found and what cross reactions can occur. I started her on a food elimination program.

I also spoke with Dr. Alexander Fisher regarding this case. He suggested that I patch test to balsam of peru, along with a dime-size piece of orange peel (inside and outside). This should be left on 20 minutes, then removed and the patient watched for one hour. Dr. Fisher did say that it is possible to have an anaphylactoid reaction from absorption to contactants. Therefore I am holding off on the patch testing.

I advised her to continue carrying her Ana-Kit at all times. I scheduled a followup visit in three months.

Claude A. Frazier, M.D.
Doctor's Park
Asheville 28801

Lessons in Medical Care From Outside North Carolina

To the Editor:

I have just returned from a two-week trip to Israel (my first) and would like to share some impressions that were gained. The trip centered around two professional experiences and a multitude of personal ones, all of which helped me appreciate the depth of the dilemma posed by the Middle East and its problems.

A. The first professional task, and the main reason for my going, was to visit the Ben Gurion University School of Medicine in Beersheba to watch the evolution of the Primary Care Program in that school. In visiting this school and program, I was able to be with young Israeli professionals as they worked in an exciting young university, in an area of the country which represents "the frontier" and in a program exploring positive change. The reality of much military presence, the reminders of recent past wars and losses, the possibilities of future attacks (daily air-raid drills for the school kids) and the disruptive requirement of military duty (being called up for the reserves up to age 55) on hospital and clinical staffing was quite evident.

The current economic crisis, with all wages lagging behind the 190% per year inflation rate, and the disruption that economic disorganization and diminishing buying power brings were evident. The earning power of professionals in the Israeli system is severely limited (around $600 per month for teachers and physicians) while the cost of living is about the same as in the United States. There is a real sense of disorganization on the economic scene, with no strong proposals receiving much publicity.

The drains on the economy from maintaining the Israeli Army in Lebanon and from the development of the West Bank area are recognized as major costs that could be removed. None the less, the forces which led to these drains remain, and seem to be psychologically dominant. The lack of feeling of direct involvement in solving these questions and opening up greater rewards for professionals is only a small part of the general frustrations of the physicians with whom I talked. The governmental system in Israel, which involves voting for a party (not a person who would have to answer to his electorate), adds to the feeling of impotence.

Most of the two weeks in Israel was spent in Beersheba in the Primary Care Unit of the Ben Gurion University School of Medicine. This unit, part of the Department of Community Medicine, is interested in developing viable and interesting careers in Primary Care for Internists, Pediatricians, and Family Physicians (and secondarily improving primary care for the people). This is the context of a Health Care System which traditionally has strictly divided preventive, maternal and child health, and mental health services (the responsibility of the Ministry of Health), primary care (delivered through community clinics developed and staffed by the Kaput Holim — the health arm of the Labor Union organization), and hospital care, delivered in hospitals operated by either the Kaput Holim, the University, or the Ministry of Health (or in some instances private organizations). This organizational scheme tends to fragment care concepts such as "total," "continuing," and/or "holistic," and tends to limit the scope and professional responsibility and the possibilities for growth of the professionals involved. Added to this are the accumulated layers of bureaucracy, policy, and administration leading to suppression of initiative in such a structure.

Ben Gurion University School of Medicine and its teaching hospital provide a potential answer to these problems, as the three groups involved (the University, Kaput Holim, and Ministry of Health) are interacting under an administrative agreement and structure that allows the Dean of the Medical School authority for change.

There are many differences in the needs of the populations served by Ben Gurion. The rapid growth of Beersheba and the development of the Negev Desert through the development of new kibbutz and moshav communities and the new towns and suburbs bring to light medical care needs engendered by the psychological stresses of resettlement, culture shock environmental factors, as well as the expected problems of neglected chronic illness. The population is generally younger. There seem to be less alcohol-related problems. The positive psychological force of community (national) purpose has, up until now, offset problems of unmet expectations.

There is a particular population subset that Ben Gurion is exploring ways of serving, namely the Arab/Bedouin population in the Negev. These people are, in one generation, changing from a nomadic, sheep-herding, tent-living life style to a monetary based, Arabic part of a Hebrew speaking Jewish country. The problems of this predictably wrenching transition are immense, but already improvement in measurable health outcomes (like infant mortality) has been achieved. From a social anthropology point of view, this is the population with the most rapidly changing needs, and represents a population group in Israel that perhaps can be brought into the main stream without the tensions extant in the other Arab groups in the country.

Medically, the University is attempting to "open up" the possibilities for a new professional style for primary physicians which will not only improve primary care, but make it a visible and sought after career opportunity.

At this time the "experiment" consists of placing recent graduate M.D.'s into a primary care clinic setting for 1-2 years before their formal residencies in internal medicine, pediatrics, or family medicine to explore the realities and to have supervised, responsible experiences in ambulatory care. This is being done in the Yoachim community (which is a community that is under much stress as a "failed-failing" socioeconomic entity), and in clinics in Beersheba. These clinic experiences are being augmented by didactic exercises weekly in the University.

They also involve association with and supervision of undergraduate medical students, but so far have not received any qualification as credit in any residency program. The value of a primary care experience in sharpening clinical skills was evident in the graduates of the program encountered in the hospital ward. Regular residents in Internal Medicine in the hospital, however, did not have access to or regular training in ambulatory care — either of previously hospitalized patients or of patients seeking primary care for medical conditions. It was also evident that the level of technology under the direct control of and easily accessible to those working in the primary care setting was limited. Hence, "ambulatory" care often, of necessity, became "hospital" care, and those responsible for the primary care did not carry the responsibility on into the hospital. I realize that the current system clearly separates these physician functions — but it leads to inefficiencies and a sense of professional isolation for those doing the ambulatory care.

This, in my mind, is the major improvement that can be made in the experience in training in primary care. If the continuum of medical care responsibility can be extended into the hospital and back out, the goals for the medical care rendered can be clarified.

The "experiment" and the goals behind it are to be commended, and the movement and development in the model have started the process of attracting young physicians to this style of medicine. Overriding these "internal" facts, however, are the external pressures on medicine and the rewards for being in the profession that may negate these good things. The "physicians' strike" last year really hurt the image of the profession (as judged by both medical students and faculty), and the means of rewards for physicians in the economic system — which is becoming unravelled — seems to discourage many of the young people. This can only be offset by pride and community within the profession.

B. The second professional opportunity came on visiting Jerusalem and being with Dr. Ted Tulchinsky in the Ministry of Health. He allowed me to become immersed in the health care needs of the Arabs and on the West Bank, and in efforts to meet those needs (as well as meet and talk with students and faculty in the School of Public Health at Hadassah). This was a most enlightening and intense experience, and it offered me an intense seminar in Arab-Jew relationships, the psychology (anguish and hatred) of an "occupied" people, and the evolution of a modern medical care system for the people of the West Bank. I visited the new (sparkling and beautiful!) clinic in East Jerusalem generated by Mayor Teddy Kollick which tries to cut across the preventative/therapeutic bureaucratic split in the health care services in Israel. It also, because of its ambience and convenience, is attracting Jewish patients for its services — a first step in breaking the Arab-Jew segregation?

The visit to the Arab hospital in Bethlehem afforded

some dramatic experiences highlighting the problems of providing modern medical care in a bureaucratically segregated system that is trying to set economic priorities for health care goals. A young Arab (ex-medical student) patient, who was transferred into the general hospital from the mental hospital, died while we were making rounds. The physicians — trained in the biomedical model — formulated the medical problem and its solution in terms of technology not available to them. The administative barriers to transferring this patient to the Hadassah Hospital I.C.U. (the patient was uninsured, the Beit Jallah Hospital had already "used" its 8 transfer slots for the month, etc.) were vividly displayed and highlighted many of the "delivery" problems for the West Bank people.

Since the 1967 War, there has been marked improvement in medical care, with improvement in all outcome measurements. Along with this has been gradual incorporation of the people (and physicians) into the system with almost 50% of West Bank Arabs having health insurance at this point. I was able to participate in a specialty clinic (Hematology/Oncology) at the Beit Jallah Hospital where Dr. Horne, a Jewish physician, brings his team of Arab fellow-residents and sees the patients in the area. This team holds clinics in the other hospital in the West Bank, and is another instance where medicine might break down the barriers between Arabs and Jews.

Unfortunately, the mind set of "occupied territory-enemy country" seems pervasive, and though many missionary types like Tulchinsky and Horne are working away, there are counter-forces that seem to overshadow them. I hope their efforts dominate.

In summary: this trip was a most instructive immersion into the health care system of training for Primary Care in Israel, as well as a look at Arab/Israeli tensions via a look at health care on its West Bank. Israel is an inspiring and wonderful country. I have faith that the historical and deeply rooted animosities can be overcome, and that the good things I saw in Israel can be spread throughout the Middle East.

James A. Bryan II, M.D.
Department of Medicine
Chapel Hill 27514

Disposing of Radioactive Waste

To the Editor:

I am writing to ask your assistance in notifying your readership about the American College of Nuclear Physicians (ACNP) Professional and Public Information Program and the important issues of Nuclear Medicine and related low-level nuclear waste disposal. The ACNP is striving to educate the non-nuclear medical community and referring physicians about these topics by providing members of our Speakers Bureau — without charge — for major meetings of all medical specialty societies, state and major county medical societies, and other health-related organizations.

Since almost all medical research involves radioisotope techniques, these topics have a direct impact on all practicing physicians. The proper understanding of Nuclear Medicine and the low-level waste issue is critical to the continuity of clinical practice and to the future of medicine. Despite its many benefits, the average patient erroneously fears Nuclear Medicine because it involves the use of small amounts of radioactive materials.

The low-level radioactive waste generated by Nuclear Medicine and biomedical research must be transported and disposed of at licensed disposal sites. Currently there is a critical shortage of these facilities. According to the Federal Low-Level Radioactive Waste Policy Act of 1980, each state must pass legislation either to enter into a regional compact for disposal or to establish its own facility by January 1986 or the generation of waste within its boundaries must stop.

Although physicians and patients want the benefits of advanced medical technology many oppose the concept of disposal sites due to their fear of radiation. If, however, the waste management problems are not solved, the practice of Nuclear Medicine and much basic medical research will be in jeopardy. Your prime readership is in a position to disseminate accurate information and address misconceptions when questioned by patients or the public about these issues.

If you are interested in writing about these issues or publicizing our Speakers Bureau, please contact me at (202) 857-1191. I will be happy to make arrangements for you to interview one of our speakers or provide you with additional information.

Barbara C. Teele
1101 Connecticut Avenue, N.W.
Washington, D.C. 20036

Two Letters to Walter Kempner

Dear Dr. Kempner:

I just want you to know how much I enjoyed your nice article, Hands Across The Sea: The Durham Connection to Germany [NCMJ 45:25-26, 1984].

I am sure that you now look back on the years 1927-1928 spent with Dr. Warburg as among the most interesting and most satisfying of all of your experiences during your brilliant career.

Kenneth Pickrell, M.D.
2609 North Duke Street
Durham 27704

Dear Dr. Kempner:

Bob Gutman just sent me a copy of your article, Hands Across The Sea: The Durham Connection to Germany. I thought you might like to hear my story about that.

During my residency in internal medicine at the II. Medizinische Klinik in Munich I also was working on my Dr. thesis with Prof. Zinnitz. It was a Literaturarbeit about which I am not exactly proud, and which dealt with allergic aspects of renal disease. Zinnitz was very well acquainted with your rice diet (1950) which he used on his patients and which he told us about a lot. I also remember that he told us to never use it on outpatients because he felt, well, he knew that the folks would not adhere to it. Nevertheless, this was the first time I heard about Duke and, indeed, was really the reason why it was Duke which was first on my list when I was looking around for an academic career after finishing my residence in Pathology.

If I had retained interest in the kidneys I might have

wound up in your corner, perhaps. Actually, several times I meant to ask you if I could go on rounds with you. But, ah, for all those distractions that keep crowding one's life.

Joachim R. Sommer, M.D.
Department of Pathology
Durham 27710

Sulfites in Medicines

To the Editor:

Most physicians are aware that the ingestion of foods containing added sulfites can cause allergic-like reactions in susceptible patients. The anti-oxidant properties of sulfites (sulfur dioxide, sodium sulfite, sodium and potassium bisulfite, and sodium and potassium metabisulfite) are used to preserve the quality and appearance of the food. As of July 1, 1983 at least 90 reactions had been reported to the Food and Drug Administration (including one fatality) in both asthmatics and nonasthmatic patients with no known allergies.[1] The symptoms of reactions to sulfites can include generalized pruritis, flushing, hives, shortness of breath, wheezing, and fainting. The signs of the reaction include erythema, urticaria, angioedema, laryngeal stridor, asthma, cyanosis, hypotension, and even respiratory arrest.

Although most reactions occurred after the ingestion of foods, prescription medications may also contain sulfiting agents to prevent oxidation.[1, 2] Unfortunately, pharmaceutical products containing sulfiting agents are not presently required to list such additives on the product label, package insert or generally available descriptions of the product, since they are currently classified as GRAS (Generally Regarded as Safe) by the Food and Drug Administrtion.

Physicians should be aware that a review of generally available information about pharmaceutical products will not reliably identify safe formulations for use in sulfite-sensitive patients. A table of medications known to contain sulfites is enclosed. The Food and Drug Administration is currently considering implementing regulations that would require the identification of added preservatives on the product label.[1] In the absence of this regulatory change, reliable information about medications safe in sulfite-sensitive patients can be obtained only by contacting the manufacturer.

This recent experience with sulfite compounds provides an invaluable lesson about instances of presumed drug allergy. It seems likely that many allergic reactions to drugs, attributed to the principal component of the medication, may have been caused by seemingly safe additives. The possibility exists that patients currently considered allergic to certain drugs could safely use the active component of the medication. This possibility is an appropriate consideration in those patients who are known sulfite reactors.

Other additives and stabilizing agents are likely to be developed for use in medications in the future. Our recent experience suggests that current methods for the scientific assessment of the safety of these compounds are not adequate. Indeed, there is no evidencce that any scientific method of study and review will provide complete assurance that a drug or additive compound will not cause an idiosyncratic adverse reaction in a small, possibly genetically susceptible part of our patient population. Physicians should consider this possibility in patients who develop an adverse reaction to a medication. The active drug should not be identified as the cause of the reaction without a review of the possible role of additives.

A clear need exists for a concise statement of all the components used in pharmaceutical preparations on the product label or package insert.

Richard H. Drew, R.Ph.
C. Edward Buckley, III, M.D.
Duke University Medical Center
Durham 27710

References

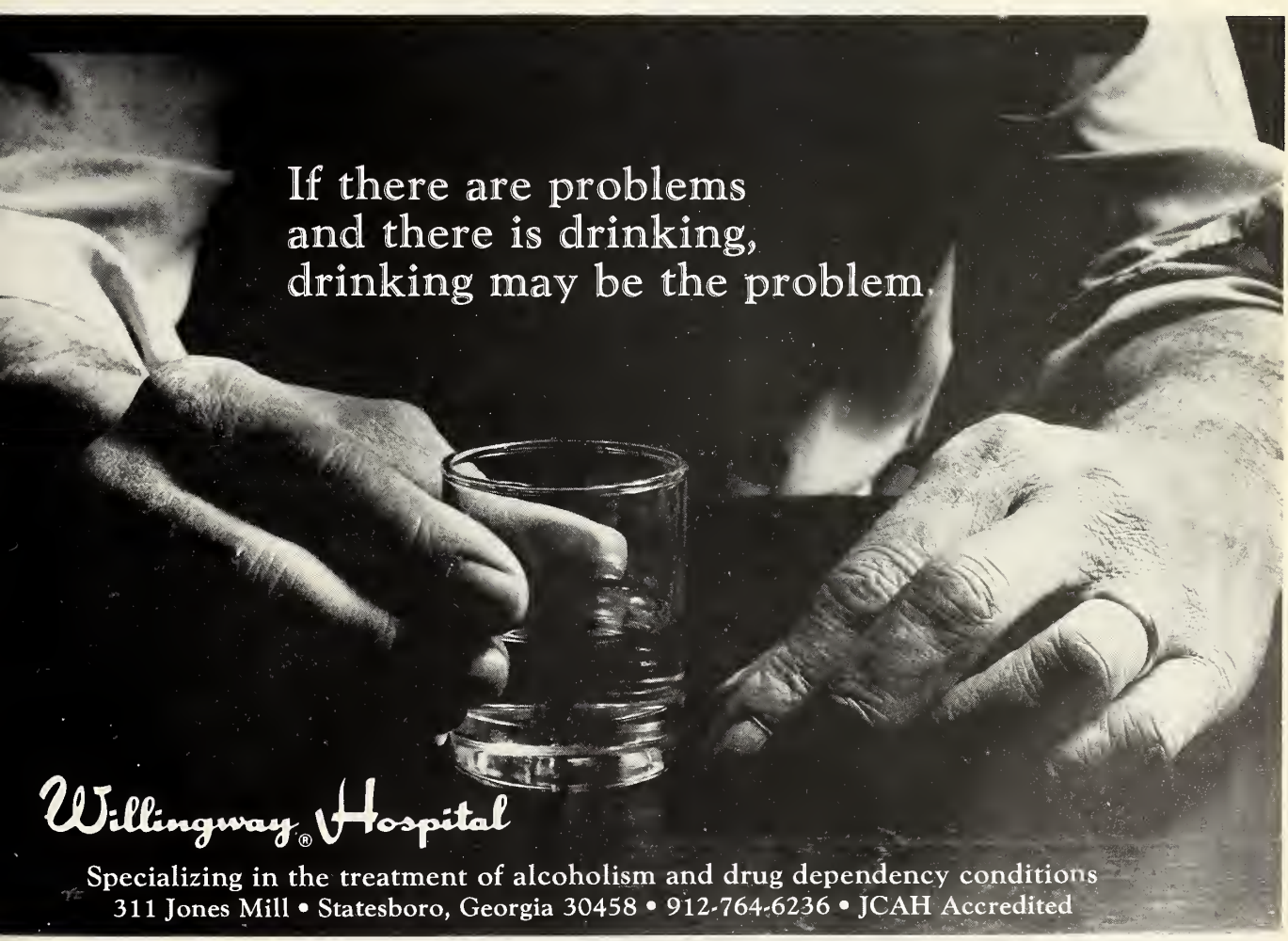
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A Partial List of Sulfite-Containing Drugs*

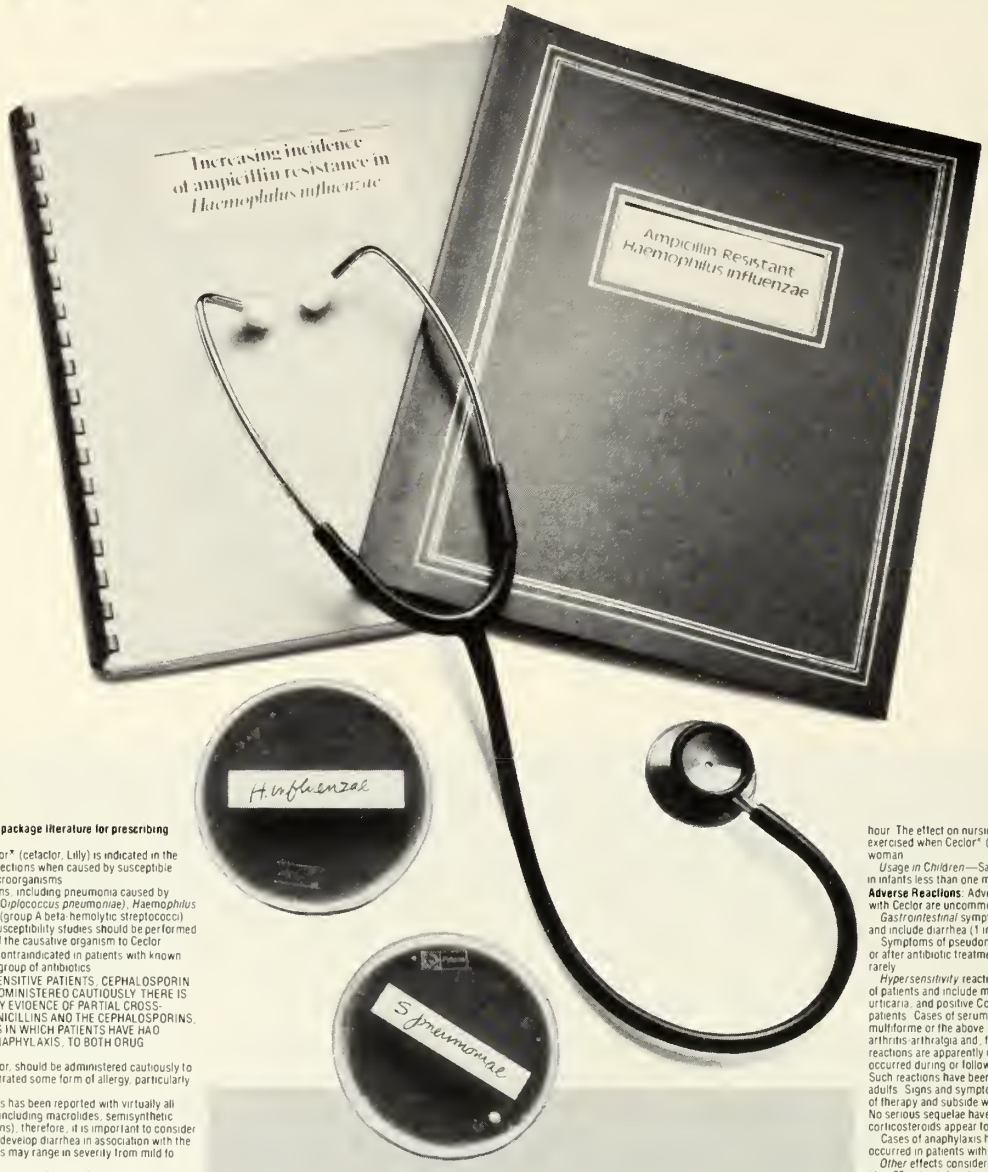
Amikacin
Amino acid solutions w/electrolytes
Amino acid solutions without electrolytes
Angio-conray
Benoxinate HCl
Betamethasone
Chloroprocaine HCl
Chlorpromazine HCl
Dexamethasone
Dextrose/electrolyte solutions
Dopamine HCl
Etidocaine
Gentamicin
Hydrocortisone
Imipramine HCl
Indomethacin
Iothalamate
Isoetharine
Kanamycin
Lidocaine HCl w/epinephrine
Meperidine HCl
Meperidine HCl and atropine sulfate
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Mepivacaine with levonordefrin
Metaraminol bitartrate
Methocarbamol
Methotrimeprazine
Methylodpa
Metoclopramide HCl
Nalbuphine
Naloxone
Neomycin/hydrocortisone/polymyxin B
Neomycin/dexamethasone
Nesacaine
Norepinephrine
Orphenadrine citrate
Perphenazine
Prednisolone acetate
Prednisolone sodium phosphate

*Unless indicated, agents are listed by generic name. For information on specific brand name products and dosage forms, consult the manufacturer.

Prilocaine
Procainamide HC1
Procaine HC1
Promethazine HC1
Propiomazine
Reserpine
Ritodrine HC1
Sodium sulfacetamide
Sulfadiazine sodium
Thiethylperazine
Tobramycin
Trimethoprim-sulfamethoxazole
Tubocurarine C1



An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor
Pulvules®, 250 and 500 mg

Brief Summary Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae* (*Diplococcus pneumoniae*), *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip; USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average peak milk levels of 1.8, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor* (cefaclor, Lilly) is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2-5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1-5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.*

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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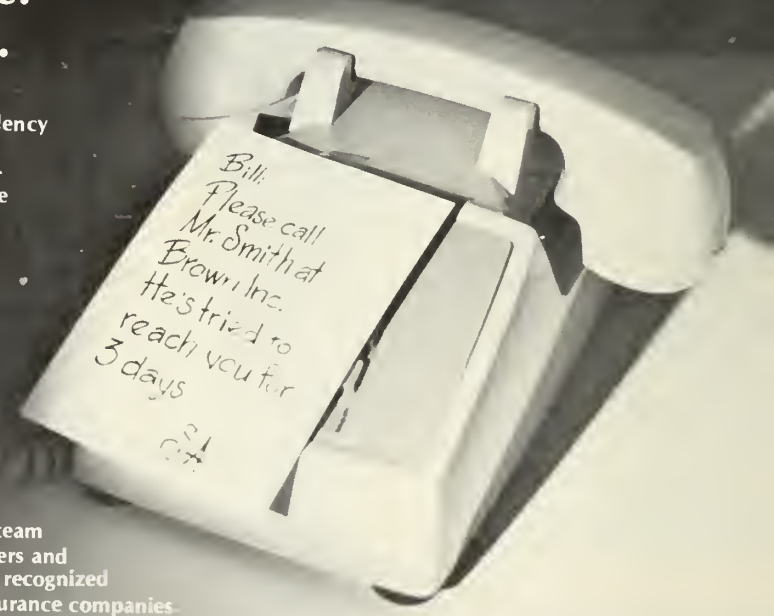
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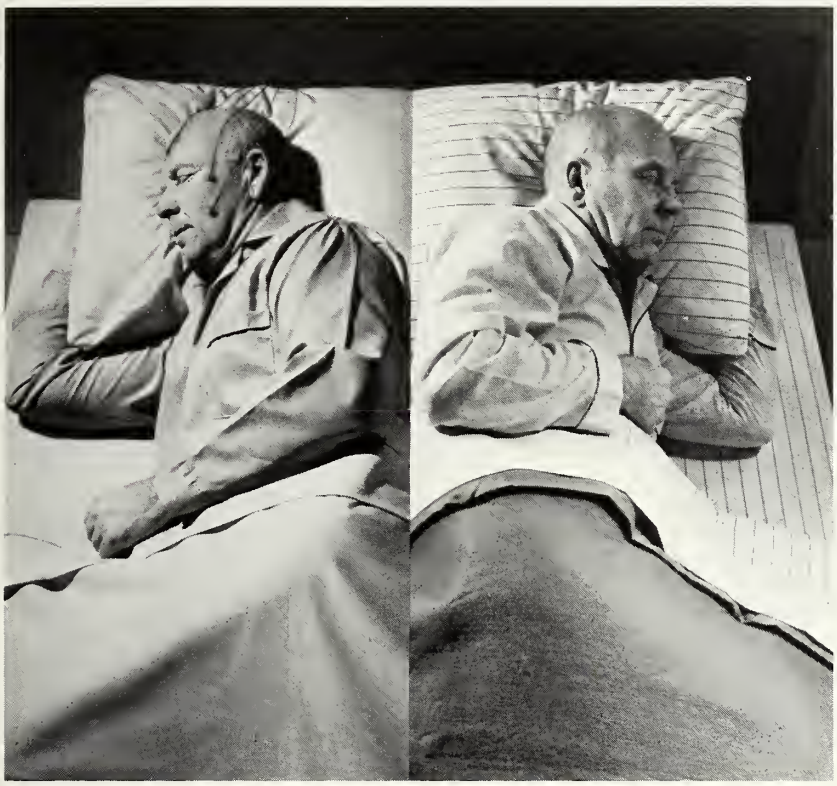


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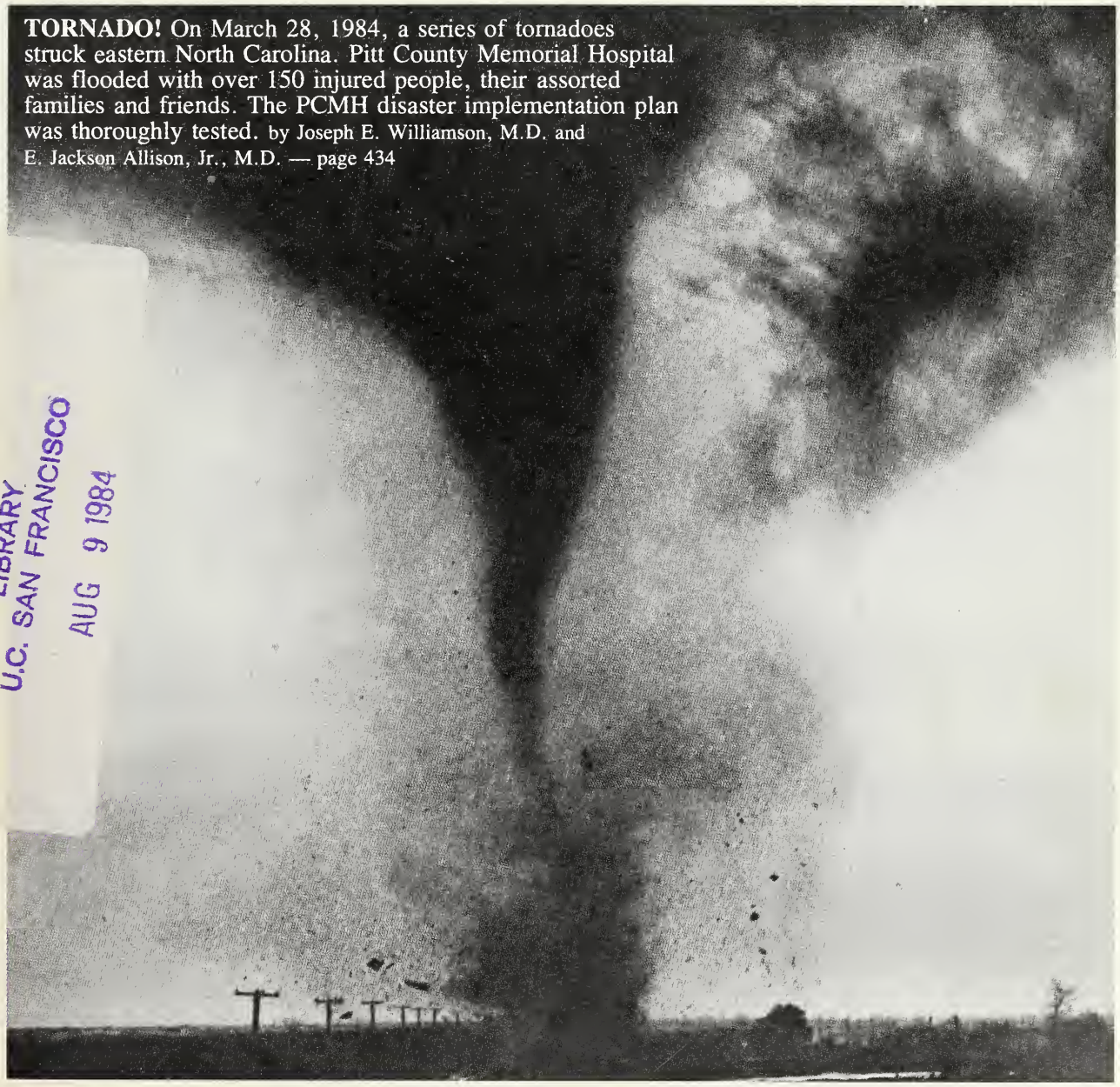
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July 1984, Volume 45, No. 7



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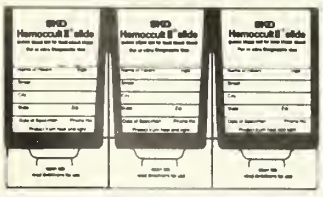
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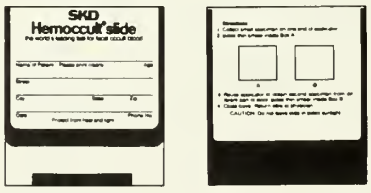
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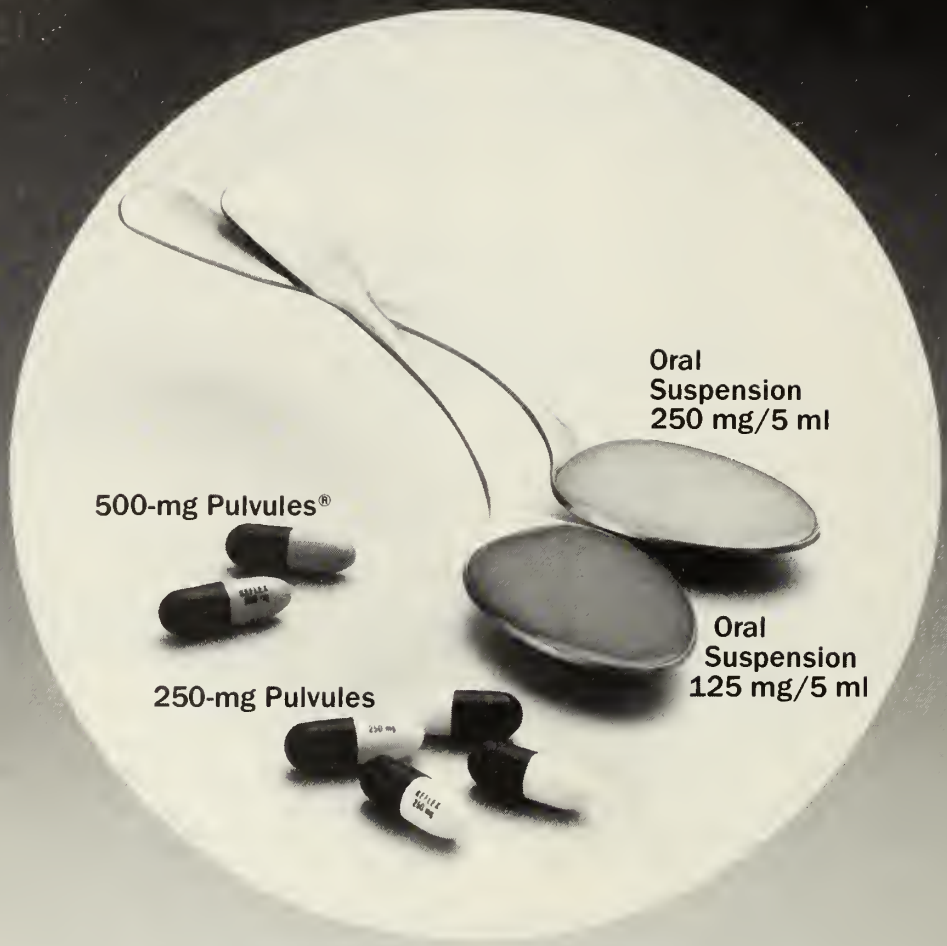
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SCIENTIFIC ARTICLE

Salmonella Choleraesuis Endocarditis

Jeffrey I. Cohen, M.D.

SALMONELLA endocarditis is rare. The majority of reported cases have been caused by *S. choleraesuis, S. typhimurium,* and *S. enteriditis*. The disease often presents acutely and may be complicated by valvular perforation, atrial thrombosis, pericarditis, pancarditis, and myocardial abscess. Most cases of salmonella endocarditis are fatal. Successful antibiotic treatment of *S. choleraesuis* has been reported only once in the literature.[1] The following report describes a second case with a favorable outcome and investigates the rationale for the choice of antibiotics.

Case Report

A 25-year-old black woman was admitted to the hospital with fever and loss of vision in the left eye. The history and physical exam showed evidence of a left central retinal artery occlusion and a new heart murmur. Blood cultures drawn the day before admission grew *Salmonella choleraesuis* sensitive to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, gentamicin, and tobramycin. Subsequent blood cultures (after treatment) were negative and a stool culture was negative for Salmonella.

Comment — *Salmonella choleraesuis* was first described in 1885 by Salmon and Smith as the hog cholera bacillus, and the first report of human infection in the United States was reported by Longcope in 1902.[2] Adults infected with *S. choleraesuis* often have bacteremia with secondary localized infections such as muscle abscesses, mycotic aneurysms, osteomyelitis, or meningitis. *S. choleraesuis* infections have a fatality rate that is five to six times higher than infections due to other salmonella serotypes.[3] There have been 10 previous case reports of *S. choleraesuis* endocarditis during the antibiotic era.[1, 4-11] Nine of the 10 cases were fatal; the only survivor was treated with penicillin and polymyxin B.

The patient's hospital course is depicted in figure 1. The patient was begun on a combination of various antibiotics and on the second hospital day an echocardiogram showed mitral valve thickening and mitral valve prolapse. No evidence of mitral regurgitation or intracardiac shunt was noted; however, fluoroscopy showed mitral valve annulus calcification. When blood culture results returned, treatment was changed to ampicillin (with acetaminophen). On the fourth hospital day a hemorrhagic lesion was noted on an index finger and a splinter hemorrhage was found. On the eighth hospital day, because of persistent fever, ampicillin was stopped and intravenous trimethoprim-sulfamethoxazole was begun. On the 10th day an echocardiogram showed a mitral valve vegetation, probable mitral valve ring abscess, pericardial effusion, and a possible tricuspid valve vegetation (similar findings were noted five days later). On the 20th day the patient was still febrile, trimethoprim-sulfamethoxazole and acetaminophen were stopped, and ampicillin and chloramphenicol were begun. Her temperature returned to normal the following day and she remained afebrile thereafter.

Comment — While salmonella are often sensitive to many antibiotics *in vitro,* these *in vitro* tests do not correspond to an *in vivo* response. Four antibiotics — ampicillin, amoxicillin, chloramphenicol, and trimethoprim-sulfamethoxazole — are effective against salmonella *in vivo.* Salmonella are often sensitive to other antibiotics including aminoglycosides and cephalosporins *in vitro,* but these drugs are ineffective *in vivo. In vitro* sensitivity testing is useful, however, in determining whether a salmonella isolate is resistant to one of the four drugs listed above.

Along with antibiotic therapy for salmonella bacteremia, most authors stress the importance of determining sites of localized infection. These include aortic aneurysms, heart valves, and myocardial abscesses. Radionuclide scanning, ultrasonography, echocardiography, arteriography, and cardiac catheterization have all been used to identify lesions involving the cardiovascular system. If an infected atherosclerotic aneurysm or heart valve is found, most authors recommend treatment with intravenous antibiotics, followed by surgical removal of the infected site and replacement by a graft or prosthesis.

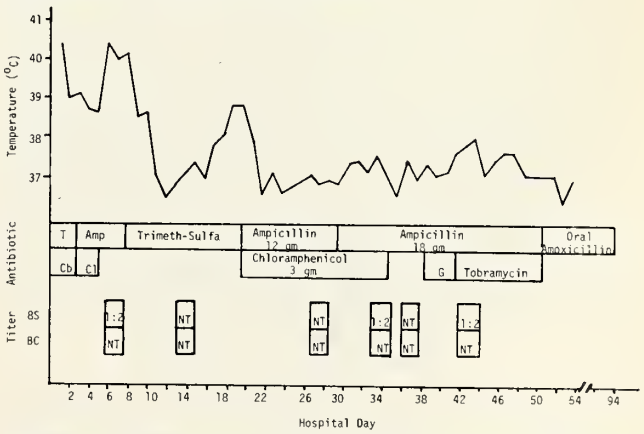


Figure 1. *Hospital course. BC = Bactericidal, BS = Bacteriostatic, NT = No titer, T = Tobramycin, G = Gentamicin, Cb = Carbenicillin, Cl = Chloramphenicol, Trimeth-Sulfa = Trimethoprim-Sulfamethoxazole, Amp = Ampicillin.*

From the Department of Medicine, Duke University Medical Center, Durham 27710.

Acknowledgment. The author is indebted to Dr. E. G. Estevez for his help in devising the time-killing curves.

On the 35th day, pancytopenia and reticulocytopenia were noted, chloramphenicol was stopped, and gentamicin was begun (later changed to tobramycin because of a skin rash). On the 36th day an echocardiogram showed no vegetations or abscess; subsequent echocardiograms were unchanged. On the 51st day intravenous antibiotics were stopped (four weeks after defervescence) and oral amoxicillin was begun. Two days later she was discharged. Oral amoxicillin was stopped after six weeks, and she remains asymptomatic six months after all antibiotics have been stopped. Serum bactericidal activity was never achieved and bacteriostatic titers of only 1:2 were obtained with various combinations of antibiotics (see figure 1).

Comment — Schlicter and McLean studied patients with endocarditis and measured serum inhibitory concentrations as the highest dilution of the patient's serum that would inhibit growth of the patient's organism.[12] This has been modified to include serum bactericidal titers, the dilution of the patient's serum (while on antibiotics) that kills the patient's organism *in vitro*. Current recommendations (for streptococcal endocarditis) suggest that antibiotics be adjusted to maintain a peak bactericidal concentration of $\geq$1:8 against the patient's organism.[13]

The patient presented above had a successful outcome despite failure to achieve adequate bactericidal activity against the organism. In a review of studies of serum bactericidal concentrations in bacterial endocarditis, Coleman et al found that none of the 17 studies showed a significant association between serum bactericidal concentrations of $\geq$1:8 and survival or bactericidal cure. They noted, however, that "each of the studies had an insufficient sample size to confidently exclude a false-negative result."[14] In order to determine why this patient responded to ampicillin and chloramphenicol, despite failure to achieve serum bactericidal titers, the patient's organism was tested further.

Methods

The interaction between the patient's bacterial isolate and the antibiotics used was studied *in vitro* by determining time-killing curves.[15] Antibiotics were prepared at concentrations that approximated peak serum levels obtainable by intravenous injection. The patient's strain of *S. choleraesuis* was incubated to turbidity and then diluted in brain heart infusion broth to a final concentration of 10^5 colony-forming units/ml. The organism was incubated at 35°C with (1) ampicillin and chloramphenicol, (2) trimethoprim and sulfamethoxazole, and (3) sterile water (control). The final concentrations of antibiotics were ampicillin 28 mcg/ml, chloramphenicol 10 mcg/ml, trimethoprim 9 mcg/ml, and sulfamethoxazole 100 mcg/ml. At 0, 2, 4, 6, 8, and 24 hours samples were withdrawn, diluted, and placed on blood agar plates. Colonies were counted after incubation for 24 hours.

Results

Figure 2 shows a plot of the time-killing curves obtained with the patient's isolate and the two antibiotic combinations. Initially there was a decline in the number of bacteria with the ampicillin-chloramphenicol combination; however, with time there was a marked increase in the number of bacteria. This may have been due to inactivation of antibiotic during incubation or selection of resistant organisms. In contrast, with the trimethoprim-sulfamethoxazole combination bacterial growth was only slightly diminished when compared with the control.

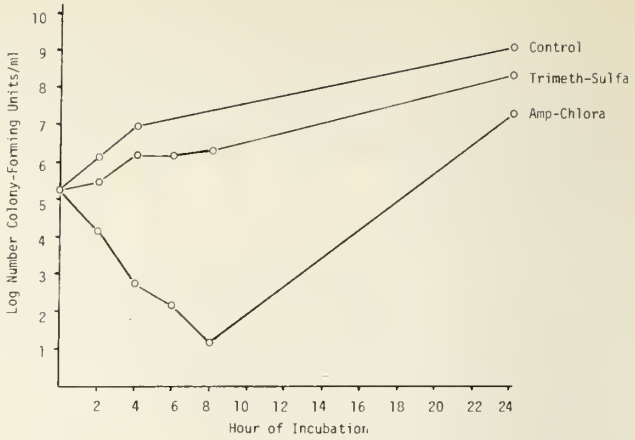


Figure 2. *Time-killing curves. Trimeth-Sulfa = Trimethoprim-Sulfamethoxazole, Amp-Chlora = Ampicillin-Chloramphenicol.*

Discussion

This patient had *S. choleraesuis* endocarditis and initially defervesced with trimethoprim-sulfamethoxazole. Subsequently, however, she had a relapse which responded to therapy with ampicillin and chloramphenicol. Analysis of serum bactericidal concentrations was not helpful in determining antibiotic therapy in this case. Instead, an alternative approach was used — measurement of the *rate* of killing of the patient's organism by two antibiotic combinations. Analysis of time-killing curves using the patient's bacterial isolate and the two antibiotic regimens showed that ampicillin-chloramphenicol resulted in a decline in the number of bacteria; trimethoprim-sulfamethoxazole only diminished the rate of growth.

These experiments thus helped to explain *in retrospect* why one antibiotic combination succeeded while another failed. In treating this patient the physicians tried a series of antibiotics known to be effective against salmonella *in vitro* and *in vivo*. While specialized tests (analysis of serum bactericidal concentrations) were tried, other clinical and laboratory signs (defervescence and fall in white blood cell count) were used in monitoring antibiotic therapy.

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SCIENTIFIC ARTICLE

Disaster Plan Implementation: Tornadoes Strike Eastern North Carolina

Joseph E. Williamson, M.D. and E. Jackson Allison, Jr., MD/MPH

• *Pitt County Memorial Hospital put its disaster implementation plan into action when tornadoes struck eastern North Carolina on March 28, 1984, killing 44 people and injuring over 800.*

WITH a tornado warning in effect, at approximately 9:25 p.m. on the evening of March 28, a tornado touched down initially in the Scuffleton community in Greene County, southwest of Pitt County, and essentially remained on the ground throughout its course through the southern areas of the county. Its course covered approximately 22 miles through more densely populated areas around Ayden, Simpson and the Portertown section, south of Greenville. The path cut by the tornado ranged from one-fourth to one-half mile wide.

Pitt County is served medically by Pitt County Memorial Hospital (PCMH), a 570-bed institution affiliated with the East Carolina University School of Medicine. It is a Level II Regional Trauma Center.

Initial Field Response

Area rescue squads began responding to calls for help at approximately 9:25 on the evening of the 28th, almost immediately after the tornado had struck. Local volunteer rescue squads from the counties of Pitt, Edgecombe, Greene and Lenoir all responded to the call, as well as rescue vehicles from the city of Greenville. It was initially very difficult to determine the extent of the disaster because of the windy, rainy weather and the fact that it was night. This disaster differed from others in Pitt County and across the state and nation in that there was no localized, circumscribed disaster scene. Victims were scattered over a 10-to-12-mile radius.

This lack of a well-defined disaster site as well as the weather conditions and darkness led to one basic change in the way the disaster was handled. Normally, in any local disaster a physician-nurse triage team is transported immediately by the local sheriff's department to the field from Pitt County Memorial Hospital. On the scene, they set up a field triage headquarters and immediately begin triaging patients for transport to the hospital. This system has worked exceedingly well in disasters that have occurred in Greenville during the last year: one in March 1983, when leaking gas from a clothes dryer exploded in a Greenville apartment complex, killing one 19-year-old East Carolina University student and injuring more than a dozen others; another in April 1983, when a school bus overturned and injured 65 children, five of them seriously.

The rescue personnel involved in the tornado disaster were all basic EMTs or EMT-Intermediates. With the lack of a physician-nurse triage team in the field, triage was carried out by senior EMTs on the scene according to protocols developed by the Department of Emergency Medicine at East Carolina University School of Medicine/Pitt County Memorial Hospital. The triage efforts by these EMTs went exceedingly well, with a majority of the patients with life-threatening but salvageable injuries being transported to the hospital first.

Internal Response

At 9:00 p.m. the emergency department at Pitt County Memorial Hospital was relatively quiet. By 9:30 p.m., it was evident that a tornado had struck the southern end of the county, although the extent of damage and personal injury was not known. It took 10 to 15 minutes before the first rescue squads arriving at the various scenes of the disaster relayed an approximation of the damage. At this point the emergency attending physician on duty immediately activated the hospital's internal disaster plan: machinery was set into action to rapidly call many of the physicians as well as nursing and other personnel to the hospital. Within 30 minutes, at least 30 physicians and over 500 hospital employees from various departments including nursing, social services, respiratory therapy, administration, central supply and the cafeteria arrived at the hospital.

As physicians arrived in the emergency department, they reported to the physician coordinator in the emergency department who assigned them according to their specialty and skills to various areas within the department. This same procedure was followed with nursing personnel, who reported to a nursing supervisor in the emergency department. Security maintained and policed the area and directed family and friends to the cafeteria. A temporary morgue was set up immediately adjacent to the hospital morgue.

The first patients to arrive at the hospital at about 9:30 p.m. were actually brought directly to PCMH in private cars by friends, relatives and family. Rescue squads began

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transporting their first victims to the hospital by 9:45 p.m. Between 10 p.m. and 2 a.m. the hospital's emergency department handled more than 150 injured individuals and admitted 29 people. Many of the latter were in critical condition. Four people died where they were struck that evening; a fifth individual was found dead the following morning. Four more patients died in the hospital, three in the emergency department and one in the operating room.

Patients had two methods of access to the emergency department. The first was through the ambulatory entrance to the department and this was used only by those patients who were brought to the hospital by their families in private automobiles. All subsequent admissions to the hospital by rescue squad came in through the rescue entrance. Physician-nurse teams skilled in triage were placed at both entrances to the emergency department and patients were triaged as they entered. These triage teams had some idea of what they were going to receive because the rescue squads had called in ahead of time over the radio giving their assessment of their patients' injuries.

As patients were triaged at the entrance to the emergency department they were assigned to areas in the department corresponding to the seriousness of their injuries and the stability or instability of their vital signs. The hospital's internal disaster plan assigns physicians, nurses and other ancillary personnel to the various areas of the department to which patients are sent after being triaged.

As patients entered the ED they were given an identification band and this information was then transferred to a master list. Patients' families and friends were diverted from the emergency department to the hospital cafeteria where members of social services and hospital administration worked with them throughout the night. By 1:00 a.m. approximately 500 friends and relatives were waiting in the cafeteria.

Later, as patients were being discharged from the emergency department or admitted to the hospital, an open line of communication was set up between the emergency department and the cafeteria. As a patient was ready to be discharged, the staff in the cafeteria would be contacted and the family would be brought to the emergency department waiting room to talk with the patient and the physician in attendance.

Within two hours after the tornado touched down, more than 100 victims had been admitted to the emergency department. Because of this heavy patient load we had to transfer patients who were more ambulatory to other areas of the hospital. As had been prearranged in PCMH's disaster plan, the ambulatory medical surgical unit was used and about 15 patients under the care of three physicians and several nurses were triaged there. One of the medical wards was partially cleared and it, too, was used for ambulatory patients.

No inpatients had to be discharged from the hospital. As patients were evaluated and their needs determined, phlebotomists stationed in the area drew blood for typing. Fortuitously, there was no severe strain on the blood bank. These patients then were transported when appropriate to the Department of Radiology which is contiguous to the emergency department. Other patients underwent portable x-ray procedures in the emergency department. Eight operating room suites were held in readiness during the disaster, and four of them were used at one time. The renal transplant team was working during the entire disaster on a previously scheduled transplant operation.

Problems and Recommendations

Several problems were noted during the course of this disaster, most of which were in some way dependent upon the severity and the size of the event. Almost two and one-half times as many injured patients were treated during this disaster as in any prior emergency situation in the hospital's history.

The initial problem was one that no one could do anything about: there was no circumscribed disaster site. Therefore, our normally functioning plan to send a physician-nurse triage team to the field proved useless. However, the EMT personnel trained in triage techniques handled on-site triage more than adequately. Another problem at the scene which added difficulties was the fact that many phone lines were down in the area.

One of the major difficulties in the emergency department with such a large number of patients was that of identifying and tracking patients. Patients were entering the hospital at two different entrances and therefore were receiving identification tags at two sites. This made compilation of a master list of patients in the emergency department somewhat cumbersome.

As the disaster progressed and as more ambulatory patients were by necessity moved to other areas of the hospital (including to x-ray, to the ambulatory medical surgical unit, to the regular medical floors by admission, and to the operating room), keeping track of patients' whereabouts became extremely difficult. We have no ready solutions for this situation, but some means of identifying and keeping track of a patient throughout the disaster is essential. We find our "area assignment" method effective in efficiently assigning personnel and in categorizing patients. However, we have found in previous disaster situations that more ambulatory patients tend to be left unattended while more severely injured patients are being treated.

Because of the large numbers of medical and nursing personnel on the scene the night of this disaster, we found it appropriate to do a great deal of one-on-one assignments, that is assigning one nurse and one physician to one or two patients. This system seemed to work extremely well because the physician-nurse team tended to follow through on a patient's care in a much more thorough way than through general area assignments.

Another transient problem arose with the Blood Bank. When the disaster began our Blood Bank had only ten units of O negative universal donor blood on hand. Our pathologists wanted to save this blood for those patients requiring immediate transfusion(s). However, patients were not typed rapidly as they entered the hospital, so initially obtaining type-specific blood was rather delayed. This situation was rectified as the disaster progressed: the pathologists stayed near the triage area at the door, and as severely injured patients arrived, phlebotomists were immediately assigned to draw the patient's blood for typing, resulting in the more immediate availability of type-specific blood.

Another problem that arose during this disaster was the scheduling of x-rays. Critically ill patients in the emergency department who needed x-rays immediately underwent portable procedures without difficulty. However, the bulk of the patients who were judged able to be transported to x-ray were not adequately differentiated according to how urgent their need for x-rays really was. We acutely felt the need for some system of assigning patients for x-rays so that the more critically injured patients were served first.

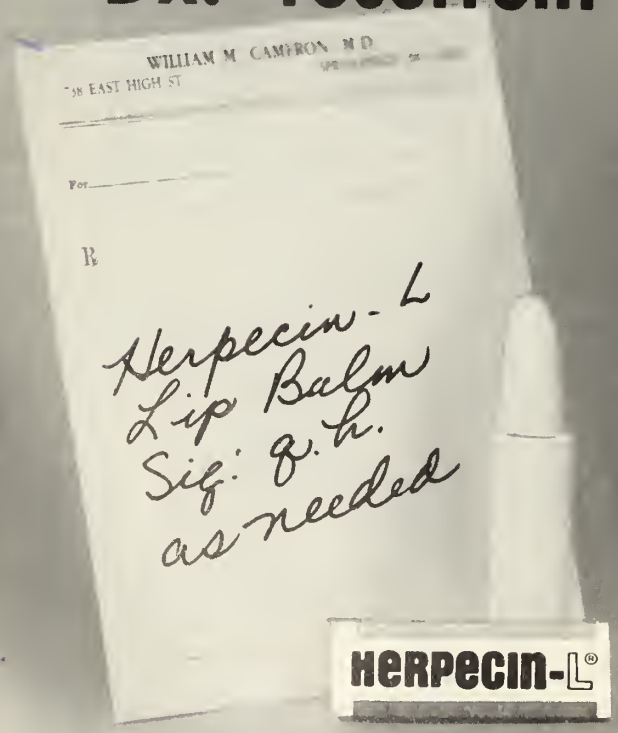
Handling of patients' families, friends and relatives in the hospital cafeteria (more than 500 individuals) went extremely well during this disaster. The Department of Patient and Family Services at PCMH was primarily responsible for this aspect of our disaster plan. Two problems were noted, however. First, there were not enough outside telephone lines in the cafeteria for the families to phone other relatives and friends in the community, which created some anxiety among those waiting. Second, there were problems with communication between the cafeteria and the emergency department as patients were ready for release, or if general information concerning patients needed to be communicated. Two systems were tried: initially, an open phone line between the two locations was used, which was unfeasible; later, a walkie-talkie system was employed with some success.

Conclusion

Our hospital's response to the disaster of March 28 was gratifying. Patient care was excellent and expeditious. However, as in any such situation, many areas for change were noted. While a certain amount of flexibility and "fly by the seat of your pants" behavior is necessary and probably essential in a disaster situation, none of this can or will take the place of adequate disaster planning. Pitt County Memorial Hospital is presently revising its disaster plan to effect improvements in the areas noted above.

It has been said that we experience God's love most fully through the expression of love we share with one another. The citizens of eastern North Carolina were indeed witness to the abundance of God's tender mercies on and since March 28, 1984.

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SCIENTIFIC ARTICLE

The Impact of Low Birth Weight on North Carolina Neonatal Mortality 1976-1982

Paul A. Buescher, Ph.D., Richard R. Nugent, M.D., M.P.H., and Ronald H. Levine, M.D., M.P.H.

INFANT mortality is an important problem in both the United States and North Carolina. In 1978 the United States ranked 17th among industrialized Western nations in terms of low infant mortality,[1] and the State of North Carolina has one of the highest infant mortality rates in the United States.[2] Neonatal mortality (deaths between birth and 28 days of age) is a large component of infant mortality, accounting for 69 percent of 1980 North Carolina infant deaths.[3] Of these neonatal deaths, 63 percent occurred under one day of age and 86 percent occurred under 5 days of age.

One of the most important factors contributing to neonatal death is low birth weight.[4-6] In North Carolina in 1980, 71 percent of infants weighing less than 1000 grams died before 28 days of age compared with 0.2 percent of infants weighing over 2500 grams. Therefore, in comparing overall neonatal mortality rates between areas, it is important to control for differences in birth-weight distributions before drawing conclusions about the relative levels of mortality risk. This is very similar to standardizing or adjusting crude death rates for differences in age distribution. Guyer et al[1] recently standardized the Massachusetts neonatal mortality to the birth-weight distribution of Sweden and found that the resulting rate was 3 percent lower than that of Sweden, compared with a crude (unstandardized) Massachusetts neonatal death rate 58 percent higher than that of Sweden. In this paper we will compare North Carolina neonatal mortality with that of the United States in a similar manner, and assess the contribution of changing birth weight to neonatal mortality trends in North Carolina since 1976.

Method

The primary statistical method used in this study is birth-weight standardization by the direct method. In this calculation, birth-weight-specific neonatal mortality rates are weighted according to a hypothetical or "standard" distribution of birth weights. For example, multiplying the North Carolina death rates for each birth-weight category by the number of births expected if North Carolina had the same percent distribution of births by weight as the United States would yield a certain number of expected neonatal deaths. Computing an overall neonatal mortality rate using this expected number of deaths allows assessment of how much birth-weight distribution contributes to the higher overall neonatal mortality observed in North Carolina.

Neonatal deaths by birth weight are derived annually in North Carolina by automated and manual matching of each infant death certificate to the infant's birth certificate, from which birth weight and other infant as well as maternal information is obtained. Reports are received for events occurring in surrounding states that involve North Carolina residents, so that virtually all North Carolina resident neonatal deaths are included.

Birth weight is more than just a measure of grams. "Since birth weight serves as an intermediate outcome for many variables associated with infant mortality, birth weight can be viewed as a summary measure of the effect of these social and demographic risk factors."[7] Low-weight infants include those born too early (low gestational age) as well as those born too small due to intrauterine growth retardation. Low-weight infants are highly susceptible to a variety of life-threatening conditions. Although a combined measure of gestational age and birth weight might be the most appropriate indicator of prematurity, there is considerable rationale for focusing on birth weight as a single outcome measure. Birth weight alone has been shown to explain the variance in neonatal mortality almost as well as a combined index of gestational age and birth weight. Furthermore, vital statistics data on gestational age have been less reliable than the birth weight data, and nonresponse is high.[7] While greater birth weight may not prevent problems such as congenital anomalies, and very heavy babies may have special problems of their own, in most cases birth weight is a very good measure of survival potential.

Wilcox and Russell[8] have suggested that standardizing neonatal mortality for birth weight is biased against the population with higher birth weights. For example, the standardized neonatal mortality rate of the population with lower birth weights will be understated if the standardization is based on the birth-weight distribution of the population with higher birth weights. Their argument assumes that the schedule of weight-specific mortality weights of a population is primarily a function of the mean birth weight, and that increasing the mean birth weight (as is hypothetically done in standardization) would necessarily involve a corresponding shift in the weight-specific mortality rates.

From the Division of Health Services, Department of Human Resources, Raleigh 27602.

Table 1

Standardization of North Carolina's Neonatal Mortality Rate (NMR) to the Birth-Weight Distribution of the United States in 1980*

Birth Weight in Grams	North Carolina Actual				United States	North Carolina Expected		
	No. of Live Births	% of Live Births	No. of Neonatal Deaths	Neonatal Deaths per 1000 Live Births	% of Live Births	No. of Live Births	No. of Neonatal Deaths	Neonatal Deaths per 1000 Live Births
≤ 1000	611	0.72	432	707.0	0.54	457	323	
1001-1500	637	0.75	94	147.6	0.61	515	76	
1501-2000	1259	1.49	55	43.7	1.32	1116	49	
2001-2500	4204	4.98	61	14.5	4.37	3691	54	
≥ 2501	77770	92.06	188	2.4	93.16	78702	190	
Total	84481		830	9.8		84481	692	8.2

* Crude N.C. NMR (actual) is 9.8 per 1000 live births; standardized NMR (expected) is 8.2 per 1000 live births. The 1980 United States crude NMR is 8.5 per 1000 live births.

Note: A few North Carolina births (26) and neonatal deaths (14) of unknown birth weight have been allocated to birth-weight categories according to the percent distribution of those with known birth weight.

Thus they suggest it is not reasonable to increase birth weights via standardization and at the same time hold mortality rates constant. To the extent that the weight-specific mortality rates of a population are determined by biology, medical care, and other factors that might not change with an increase in the mean birth weight, the magnitude of the bias that they propose would be reduced. In any case, adjusting the standardized rates in the present paper for this possible bias would not alter any of the major findings or conclusions.

Results

Comparison with the United States

In 1980 there were 830 neonatal deaths in North Carolina out of 84,481 live births for a rate of 9.8 neonatal deaths per 1000 live births. United States data for 1980, the latest available, show a crude neonatal death rate of 8.5,[9] which is 13 percent lower than the North Carolina rate. If, however, we assume that North Carolina births had the same weight distribution as United States births, a different picture emerges (table 1).

In North Carolina 7.9 percent of 1980 births were below 2501 grams, compared to 6.8 percent in the United States. If North Carolina had experienced the same birth-weight distribution as the United States, 932 fewer infants of low birth weight would have been born in North Carolina in 1980. Applying the United States percent distribution by weight to the 84,481 North Carolina births in 1980 and then applying the North Carolina weight-specific neonatal death rates to these births results in 692 expected neonatal deaths. Thus if the North Carolina birth-weight distribution in 1980 had been the same as that in the United States, 138 fewer neonatal deaths would have occurred. The North Carolina neonatal mortality rate would then be 8.2 rather than 9.8, a 16.3 percent reduction and below the U.S. rate of 8.5 rather than higher as actually occurred.

We conclude that neonatal mortality is higher in North Carolina than in the United States because of a less favorable birth weight distribution and, in fact, weight-specific neonatal death rates are on the whole lower in North Carolina.

Neonatal Death Rates by Race

Standardizing the North Carolina neonatal mortality rate in the manner shown above does not take into account that the percent of nonwhites in North Carolina is higher than that in the United States. On the average, nonwhites have a substantially higher percent of low-weight births than whites. If one assumes that it is not reasonable for nonwhites in North Carolina to achieve the same birth-weight distribution as the U.S. average in the near future, then the approach of doing race-specific standardization would be appropriate. In North Carolina the white and nonwhite neonatal mortality rates in 1980 were 8.1 and 13.5, compared with United States rates of 7.5 and 12.5. If North Carolina whites and nonwhites had the same birth-weight distributions as their white and nonwhite counterparts in the United States, and there were no changes in the North Carolina race-weight-specific neonatal death rates, the 1980 North Carolina white neonatal mortality rate would be 7.5 and the nonwhite rate would be 12.0. Thus, even when each race is considered separately, the higher North Carolina neonatal death rate can be attributed entirely to lower birth weights.

A very interesting finding that emerges from this race-specific analysis is that 1980 North Carolina nonwhite weight-specific neonatal death rates were *lower* for every weight category than the comparable white rates. This was also true in North Carolina for 1981, and other studies have consistently shown substantially lower nonwhite neonatal mortality rates for birth-weight categories under 2501 grams.[10-12] David and Siegel[12] suggest that this differential holds up even after controlling for differences in gestational age. Thus the higher overall nonwhite neonatal mortality rate in North Carolina in 1980 (13.5 versus 8.1 for whites) was clearly due to lower nonwhite birth weights. The percent of nonwhite births under 2501 grams was 11.9 in 1980, compared with 6.1 percent of white births. For births under 1501 grams, where neonatal mortality is especially high, the nonwhite percent was almost two and one half times the white percent. If nonwhite births in North Carolina had the same weight distribution as white births, nonwhite neonatal mortality would be 6.7 compared with 8.1

Table 2
Changes in Birth-Weight-Specific Neonatal Deaths per 1000 Live Births by Race, North Carolina 1981-1982

Birth Weight in Grams	Total				White				Nonwhite			
	1981 Rate	1982 Rate	% Change	p	1981 Rate	1982 Rate	% Change	p	1981 Rate	1982 Rate	% Change	p
≤ 1000	691.1	687.2	−0.6	.94	723.9	675.4	−6.7	.52	651.3	695.8	6.8	.47
1001-1500	110.1	132.8	20.6	.24	163.5	164.1	0.4	.98	53.5*	101.2	89.2	.03
1501-2000	44.8	33.2	−25.9	.13	55.1	43.1	−21.8	.32	30.2	23.0	−23.8	.45
2001-2500	11.5	14.1	22.6	.29	12.0	13.8	15.0	.60	10.5	14.4	37.1	.28
≥ 2501	1.9	2.1	10.5	.37	1.9	1.8	−5.3	.70	1.8	2.8	55.6	.02
Total	8.8	9.5	8.0	.13	6.9	6.9	0.0	1.00	12.3	14.7	19.5	.02

* This rate is extremely low and probably does not represent the underlying or "true" rate in 1981. The comparable rate in 1980 was 110.7.

Note: The probability (p) values indicate the probability that a change as large as the one observed could have occurred due to random fluctuations in the rates, considering the number of deaths in the numerators. For example, .02 would indicate 2 times out of 100.

for whites, assuming no change in the weight-specific death rates. However, nonwhite postneonatal death rates (i.e., deaths age 28 days to one year) are substantially higher than the white rates for every birth-weight category.

Recent Trends

1976-1980

The contribution of changing birth weights to the decline of North Carolina neonatal mortality from 12.9 in 1976 to 9.8 in 1980 was also examined. Practically none of this reduction can be attributed to increased birth weights. The percent of births under 2501 grams was 8.3 in 1976 and 7.9 in 1980. But the percent of births under 1000 grams actually increased from 0.61 in 1976 to 0.72 in 1980, with most of this increase occurring among nonwhites. Part of this increase could, however, be due to better reporting in 1980 of very low-weight deliveries as live births rather than as fetal deaths.[12] But if we apply the 1976 North Carolina birth-weight distribution to 1980 births and assume the same 1980 weight-specific neonatal death rates, the expected rate of 9.2 is actually lower than the observed rate of 9.8. Therefore, the decline in neonatal mortality from 1976 to 1980 is overwhelmingly due to reductions in weight-specific neonatal death rates. The rates in the under 1001 grams, 1001-1500, 1501-2000, 2001-2500, and greater than 2500 grams birth-weight categories declined by 17, 49, 47, 36 and 24 percent, respectively, over this period. These decreases in the low-weight death rates are associated with steady increases in the percent of low-weight births occurring in Level III (tertiary care) hospitals, where weight-specific death rates decreased from 1976 to 1980. Among births under 1500 grams, the percent occurring in Level III hospitals was 39.6 in 1976 compared with 58.1 in 1980.

1981-1982

The analysis of neonatal mortality into two major components sheds considerable light on the 1982 upturn in infant mortality in North Carolina. Much has been said about the increase in the infant mortality rate from 13.2 in 1981 to 13.7 in 1982, an increase that could be expected to result from random changes nearly 4 times out of 10. Further investigation, however, reveals that *all* of this increase in the infant mortality rate was due to an increase in neonatal mortality, and in fact all of this increase in neonatal mortality was among nonwhites. Neonatal deaths increased from 739 in 1981 to 813 in 1982, or from 8.8 neonatal deaths per 1000 live births to a rate of 9.5 in 1982. The postneonatal death rate declined slightly from 4.4 in 1981 to 4.3 in 1982. Looking at this by race, the white neonatal mortality rate was 6.9 in both 1981 and 1982, while the nonwhite rate increased from 12.3 to 14.7.* We would expect this 20 percent increase in the nonwhite neonatal death rate to occur due to random changes less than 2 times out of 100. Postneonatal deaths per 1000 live births declined by 8 percent for nonwhites, while increasing 3 percent for whites.

The increase in neonatal mortality from 1981 to 1982 was associated with a worsening of the birth-weight distribution. The percent of births less than 2501 grams increased slightly from 7.9 to 8.0, but the number of births under 1000 grams increased by 47 from 586 to 633, or from 0.70 percent of all births to 0.74 percent. This general pattern of change is also apparent for the two racial groups. Yet the increase in the prematurity rate among nonwhites accounts for only a small proportion of the overall increase in the nonwhite neonatal mortality rate. If 1981 nonwhite births are assumed to be distributed by weight like those in 1982 (in percentage terms) and then the actual 1981 weight-specific death rates are applied, an expected nonwhite neonatal mortality rate of 12.5 results. Thus lower birth weights explain only around 8 percent of the 1981-1982 increase in the nonwhite mortality rate from 12.3 to 14.7.

An examination of changes in the weight-specific neonatal death rates from 1981 to 1982 sheds more light on this problem. Table 2 displays these changes. For total births, three of the rates increased and two decreased, though none of these changes was statistically significant at the p = .05 level. For whites also none of the changes was significant. For nonwhites, 4 of the 5 rates increased from 1981 to 1982 and two of these increases were significant at below the .05 level.† These data confirm that the increase

* The race-specific death rates using race at birth from the matched birth/infant death file, which are shown here, may differ slightly from the rates using race as assigned on the death certificate.

† See, however, the first note to table 2.

in the overall nonwhite neonatal mortality rate was due substantially to increases in weight-specific death rates. These increases in the weight-specific death rates were not associated with a decreasing percent of births in these weight categories occurring in Level III hospitals. Considering also that there were increases in certain race-weight-specific death rates from 1980 to 1981, it appears that the consistent decline of weight-specific neonatal mortality rates that has occurred since at least 1976 has temporarily abated.

Discussion

This study demonstrates that examination of "crude" neonatal or infant mortality rates is not sufficient. Birth-weight-specific mortality rates must be examined in relation to the distribution of births by weight. In order to undertake such analysis, matched birth and infant death files are required. Given that the relatively poor ranking of the United States among industrialized nations with regard to neonatal mortality is due largely to low birth weight,[4] it is difficult to justify the unavailability of such data for the entire United States for the direction of national policy.

The results of this analysis have some important implications for North Carolina policies designed to further reduce the neonatal mortality rate. Almost none of the reduction in neonatal mortality since 1976 has been due to increased birth weights. The major improvements in neonatal mortality have resulted from better medical care of small babies in neonatal intensive care units,[1, 10, 13] which has served to reduce the weight-specific neonatal death rates particularly in the 1001 to 2500 grams categories. Williams and Chen[13] suggested that the increased rate of cesarean section for low-weight infants also contributed to the decline of neonatal death rates in California. They found that decreases in birth-weight-specific mortality accounted for 85 percent of the decline of the neonatal mortality rate in the 1970s, with only 15 percent due to improvements in birth weight, and no improvement was observed in the birth-weight distribution for blacks. Goldenberg et al[10] found that only 5 percent of the nearly 50 percent reduction in neonatal mortality in Alabama from 1970 to 1980 could be attributed to changes in birth-weight distributions, and birth-weight changes accounted for 12 percent of the decrease in the white neonatal mortality rate but none of the decrease in the nonwhite rate. David and Siegel[12] found for North Carolina that "better babies," as reflected primarily in increased birth weights but also considering gestational age, accounted for 85 percent of the decline in neonatal mortality from 1968 to 1972, but accounted for only 16 percent of the decline from 1972 to 1977, with the rest of the decline attributable to better weight-specific survival rates or "better care." They also found that improved birth weights and gestational ages were a much less important factor in the decline of neonatal mortality for nonwhites as compared with whites.

It is likely that, in the near future, further major reductions in neonatal mortality will require more than efforts to increase weight-specific neonatal survival after birth, though some improvement may occur by extending neonatal intensive care services to persons who have not had access to them. The birth-weight standardization carried out above suggests that North Carolina weight-specific neonatal death rates are probably already below the United States rates. Goldenberg et al[14] have presented the lowest average weight-specific neonatal mortality rates reported in the medical literature for the 1976-1980 period, and the average 1976-1980 rates for North Carolina were 20 to 65 percent higher than these lowest "literature" rates. By 1981, however, the North Carolina annual rates were below these lowest average 1976-1980 rates for all weight categories except 2001-2500 grams, where they were equal. The trend in weight-specific rates from 1981 to 1982 (table 2) indicates that future large increases in neonatal survival rates will be difficult to attain. If we apply the 1979 Swedish birth-weight distribution to 1979 North Carolina births and assume that 1979 North Carolina weight-specific neonatal death rates would be in operation, the expected rate is 5.6 compared with 5.0 in Sweden and compared with an actual North Carolina 1979 rate of 10.4. North Carolina weight-specific neonatal death rates therefore appear to be very close to those in Sweden, which has one of the lowest crude neonatal death rates in the world.

Thus, further large reductions in neonatal mortality in North Carolina are not likely to result from neonatal intensive care and other methods that increase the rate of survival after birth, though certainly some improvements can be made in this area by extending these services to groups that have not had access to them in the past. If North Carolina is to reduce neonatal mortality to the United States average or lower, we must adopt policies that will lead to a substantial reduction in low-weight births.

The results above also show that the North Carolina racial gap in neonatal mortality could be eliminated and in fact reversed if North Carolina nonwhites achieved the birth-weight distribution of whites, with no change in neonatal survival rates. Several of the studies cited above indicate that improved birth weights have been a much less important factor in the decline of nonwhite neonatal mortality compared with whites, including the study by David and Siegel[12] for North Carolina during the 1968 to 1977 period. Goldenberg et al[10] found for Alabama that shifts in birth-weight distributions for nonwhites from 1970 to 1980 would have *increased* the neonatal mortality rate if weight-specific death rates had not been declining at the same time.

The data in the present study show a widening racial gap in neonatal mortality: the nonwhite crude neonatal mortality rate was 35 percent higher than the white rate in 1976, 67 percent higher in 1980, 77 percent higher in 1981, and 113 percent higher in 1982. The percent of nonwhite births under 2501 grams remained almost exactly twice the white percent during this 1976-1982 period (12.1 versus 6.1 in 1982), but the percent of births under 1001 grams for nonwhites changed from 2.3 to 2.9 times the white percent. Death rates in this very low weight category have not declined as rapidly as those in the 1001-2500 grams categories. The ratio of nonwhite to white neonatal death rates at each weight category did not change substantially from 1976 to 1980. From 1981 to 1982, the weight-specific death rates for nonwhites worsened considerably in comparison with the white rates, contributing to the widening racial gap (table 2). In fact, the nonwhite neonatal death rate was higher than the white rate in 1982 for three of the

birth-weight categories, whereas in 1980 and 1981 all of the weight-specific nonwhite rates had been lower. The worsening of these nonwhite rates from 1981 to 1982 in comparison with the white rates was not associated with a relatively lower percent of nonwhite births in these weight categories occurring in Level III hospitals.

These recent increases in nonwhite weight-specific neonatal death rates are cause for concern, particularly the increase in the over-2500-grams category (table 2). But there is still a critical need to reduce the high rate of low-weight births among nonwhites in North Carolina, and much room for improvement. "The intensive care approach alone will not suffice to close the racial gap in newborn mortality."[12] Williams and Chen[13] suggest that the most obvious target for sustaining the decrease in neonatal mortality rates is the reduction of low-weight births among blacks, and the data in the present study support this conclusion. Prenatal medical care strategies alone are not likely to solve this problem, since the weight distribution of live births in any population is closely linked to aspects of social class.[4] Low birth weight is strongly associated with low socioeconomic status.[5]

The application of neonatal intensive care technology has led to very rapid increases in neonatal survival rates, but strategies to increase birth weights may not show such rapid results. A number of interventions have been underway in North Carolina and are increasing, such as provision of prenatal care, nutritional supplementation and counseling, and health education. The overall low-birth-weight rate did decline from 8.3 percent in 1976 to 7.9 percent in 1981, and certainly efforts of this type must be continued. In addition, new medical care strategies such as early detection of incipient premature labor and treatment with tocolytic agents have shown some promise.[15] A large and sustained reduction of low-weight births is, however, also dependent upon the longer-term process of overall socioeconomic development and associated factors such as better education, employment opportunities, and incomes. Though these changes may be difficult to implement, they are nevertheless very important. Further improvements in neonatal mortality through postnatal medical interventions are not only limited, they are also very costly. Prevention of low-weight births will reduce not only the overall neonatal mortality rate but also neonatal intensive care costs. Sweden, which has about the same number of deliveries per year as North Carolina, has only about half as many low-weight births and neonatal deaths, and about half the number of ventilator-equipped neonatal intensive care beds as North Carolina.[12]

While the outcome measure in this study was neonatal mortality, another result of increasing birth weights would be the reduction of neonatal morbidity. Low-weight babies are at higher risk for intracranial hemorrhage and birth asphyxia.[12] Without losing sight of the positive contribution of intensive perinatal medical care in reducing morbidity,[16] "a strategy aimed at reducing the prematurity rate should be more effective in reducing morbidity in the population than a strategy focused primarily on helping premature babies survive, once factors have combined to cause a premature birth."[12]

In summary, this study has shown that North Carolina's higher neonatal mortality is due entirely to lower birth weights, when compared with the United States, and that little improvement in birth-weight distribution has occurred since at least 1976. Further, from 1981 to 1982 the percent of low-weight births actually increased. Clearly, a major part of our agenda for preventing future neonatal deaths in North Carolina should be the implementation of programs that reduce the number of low-birth-weight babies. Given the impact of low birth weight on morbidity and health care costs as well as on neonatal mortality, perhaps the low-birth-weight rate should become the major performance measure for maternal and child health programs.

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Women Doctors

Eugene W. Linfors, M.D., editor

The question for the July issue of the Journal is: **Will the increase in number of women doctors change the practice of medicine? What effect will more women doctors have on the penetration of the market by Health Maintenance Organizations?**

From Janice E. Daugherty, M.D., a family practitioner in Greenville

I think more women in medicine will improve medical care in general, but especially care for women. The more familiar a physician is with the patient's situation, the better care he or she can provide to that patient. Since the cultural milieu may be vastly different for men and women (even of similar socioeconomic and geographic origin), decreasing the "cross-cultural" nature of the health care experience can lead to improved quality of medical service. A truly sympathetic caregiver can do much to improve the patient's self-confidence in handling symptoms or disease, as well as providing guidance for life-stage situations, which often has personal experience behind it. For example, the best caregiver for a nursing mother is a physician who herself has *successfully* breastfed — especially through the trials and tribulations of nursing while employed full-time. The ability to convey the attitude that "you can do it, it won't necessarily be easy, but I'm here to help if you develop a problem you can't handle alone" will do much to erase the sometimes pathologically dependent role women have been forced into through the past use of antianxiety agents and pain pills.

Moreover, since a majority of physician visits are made by women, improving that interaction can significantly raise the overall quality of health care.

Increasing numbers of women allow changes in the way medicine itself is practiced. By seeking alternatives to the "24 hour-a-day doctor" role — necessitated by a desire to maintain a home and family as well as a medical practice — women in increasing numbers will humanize the medical profession. The need to communicate to patients that "Yes, I care about you, but I care about myself and my family also. I will be available for your needs when I can; when I cannot be available you will be cared for by a colleague whom I trust" often leads to women physicians seeking more structured practice in groups, HMOs, salaried positions, etc. Working fewer hours usually means making fewer dollars; balancing this somewhat is the fact that a majority of women physicians are in families for which she is not the sole breadwinner.

Improved lifestyle and family relationships not only affect women physicians; male physicians also benefit from the trend that allows them some freedom from "medicine as a jealous mistress." Male physicians traditionally may have hesitated to challenge the norms of medical practice; women physicians do it out of necessity.

In summary then, I see change brought about by increased numbers of women physicians as coming in three major areas: improved quality of medical care principally to women, more humane physician lifestyle with fewer total hours of practice, and lowered average physician income.

From Daniel L. Dolan, M.D., an internist in Asheville

When I hear this matter discussed in open forum, it invariably provokes heated discussion and feelings. Your query has therefore prompted me to attempt to locate some objective data, which I am happy to enclose.

Our AHEC Residency Program in Asheville is in Family Medicine, traditionally taking eight residents at each level for a three-year period. We have recently reduced to six in partial response to the perceived physician excess. I have reviewed the careers of all those in our program (which opened its doors in 1975). Our first graduating class was in 1978.

These data should not be extrapolated to other subspecialty areas since they represent only one small sample in one local Family Practice Residency Program. Traditional subspecialties attracting women physicians (such as obstetrics, pediatrics, etc.) might show different data. Nonetheless, here is an objective sampling which, in its overall, suggests that women tend to seek more part-time employment than a full-time private practice, and are less inclined to establish longitudinal on-going patient responsibilities than their male counterparts.

Dr. E. Grey Diamond has recently pointed out that women physicians, in order to have a full medical career, must have a different set of support systems at home. The spouse must take over many home responsibilities with or without hired housekeepers (E. Grey Dimond: "Women in Medicine" — Two Points of View. JAMA 1983; 249:207-210). Of interest is the fact that one of our three women physician graduates in full-time private practice exactly fits this model. She is a physician and her husband is a registered nurse who participates in a major way in the care of their two young children and the home (although he also works in a nursing role). This unusual situation is quite successful for them and proves that when such arrangements are possible, the Dimond model can be quite successful.

	Full-time private practice	Part-time employment and emergency room work	Full-time non private practice (institutional, public health, etc.)	Voluntary drop-out	Dismissed from program	Died
MALE (N=36)	25 (69%)	2 (5.5%)	4 (11.5%)	2 (5.5%)	2 (5.5%)	1 (3%)
FEMALE (N=13)	3 (23%)	3 (23%)	2 (15%)	4 (31%)	1 (8%)	0 (0%)

Lastly, I could only speculate as to the impact of women physicians on HMOs, PPAs and similar economic "market force" arrangements. From the above data, it would be reasonable to project that where large group practice arrangements are possible within these economic units, women physicians would likely be attracted to them where coverage would be liberally provided. Even where these economic units extend to many different types of practice as a loose financial federation without practice cross-coverage, I would think women's participation would be likely as an added source of income. Male physicians would be more traditionalist oriented toward private fee for service practice as long as it was financially feasible. If Minneapolis is any example, all will ultimately accede to similar arrangements if their community medical structure goes in this direction. I am not convinced that patients will benefit from these arrangements.

I do not claim erudition in the above remarks. If women physicians are less inclined to occupy full-time equivalents, the perceived over-production of physicians may be significantly lessened and future medical manpower planning should take this into consideration.

From Claude A. Frazier, M.D., an allergist in Asheville

I, personally, don't believe the increase in women physicians will make any fundamental change in the practice of medicine, unless of course, women physicians flock to a particular discipline, such as gynecology, obstetrics or pediatrics. Even then, the presence of women physicians has provided women patients, who often prefer a specialist of the same sex in these fields, a choice.

The same can be said for the penetration of women physicians into the Health Maintenance Organizations and for the dramatic increase of women in the work force these last few decades increasing the number of women cared for under Health Maintenance Organization contracts. Again the presence of women physicians offers choice, a choice no doubt greatly appreciated by women patients.

All in all, I strongly believe the increase of women physicians has had a great and good impact on medicine in general.

From Jack Hughes, M.D., a urologist in Durham

The increase in the number of women doctors will likely change the practice of medicine in at least two ways.

The first effect will be part of that total increase in the supply (or over-supply) of doctors both men and women. For example, the "over-supply" will lead to increasing competition for patients which undoubtedly will make physicians' services more readily available in the evenings and on weekends. There will be more time to spend with each patient, fewer working hours, lower incomes, etc. Health care costs will not be lowered but the rate of increase undoubtedly will be slowed.

Secondly, the practice of medicine will change to the degree that women physicians sacrifice income for regular hours, more free time to rear children, be a part-time housewife, or just enjoy time off. Such women physicians may be willing to work in salaried positions for smaller hourly incomes. HMOs, PPOs and similar groups will probably be in a better position to offer this type of employment than would traditionally structured practices and thereby be more competitive in the health care market.

But then of course most of the women physicians may become like the typical men physicians of the past and work longer hours and with even greater intensity to prove some point or for whatever reason. In which case my second point will be moot.

From Richard Janeway, M.D., Vice President for Health Affairs in Winston-Salem

Whenever I am asked what the effect of increasing numbers of women in medicine will be, I am tempted to say, "It's got to be better." That reply, although trite enough for the question, of course, is not true. In a recent survey conducted by Dr. George Rhinehart, Associate Professor of Sociology at the University of Alabama under the auspices of the National Opinion Research Center, physicians were rated second only to Supreme Court Justices as the most prestigious profession. We achieved a rating of 93 on a scale of 20-100. In 1963 and 1947, when similar surveys were compiled, physicians led the list with an identical 93 rating. Whatever else can be said about our predominantly male predecessors and compatriots, they apparently have in the main conducted themselves with honor and professionalism. I wonder, however, if that is so much a reflection of their maleness as the caliber of person that has historically been drawn to the healing art?

Will the increase in the number of women doctors change the practice of medicine? My answer to this question is a resounding yes, but no. The yes results from the biologic and cultural imperatives that affect women physicians. Let me explain.

Few young adults, if they are honest with themselves, can deny that they have considered having children. For women, this involves the necessity, aside from the rare occasions of adoption, of bearing the child. In addition, despite tremendous advances made by males in recent years

— one is even tempted to say "we've come a long way baby" — the cultural reality of 1984 is that there are still relatively few truly emancipated female or male spouses. This means that most of the time, the working woman and mother also has primary responsibility for the household. The combination of these biologic and cultural factors has, I believe, affected women's choices of medical specialties in the past. Disciplines such as surgery, that involve long hours of standing, have been seen as incompatible with pregnancy. Specialties with unpredictable hours such as obstetrics or transplantation have been avoided because of their potential impact on family responsibilities. Only multi-member private practice situations have been sought because maternity absences impact one, two or three member partnerships too drastically. Contrarily, specialties such as pathology, radiology or dermatology have been traditional favorites with women in medicine, because of the more structured nature of the practice.

In 1984 the imperatives remain, but the women have changed. So have the times. First, we are in the midst of a renaissance for young women in this country. Effective birth control which women can control has enabled women to be as sexually active as they wish without fear of an unplanned pregnancy. The women's liberation movement has shown, even forced women to consider any profession their domain. Wonder women such as Tenley Albright have shown that it is possible to win an Olympic gold medal, raise a family, and be a surgeon in the same lifetime. In short, the young women in America today have been taught that they can have it all: and now they want it. They do not believe old mores such as "nice girls are not aggressive enough to be general surgeons or deans." Today's college graduates, the women I interview for medical school, have no such reservations. They know they can find a way to do both and more. Today's woman professional is going to insist that her biologic imperative be accommodated, not delayed or denied.

Second, there are several trends in medical practice that should be attractive to young physicians of both sexes trying to combine career and family. Health maintenance organizations, prepaid practice organizations, operations such as MedFirst, and even emergency medicine positions all have the advantage of predictable hours, no call-commitment, and no dedicated patient population that must be covered during off-hours. I believe such positions will be increasingly popular with our junior peers. For women in particular, these new options will have the effect of making more specialties feasible and appealing.

Aside from the changes brought about by the biologic and cultural imperatives described above, however, it is my contention that increasing numbers of women will not change greatly the essence of American medicine, as long as our women are selected as carefully as our men. Inevitably, sheer numbers of women entering the field will result in enough experienced teachers, scientists, and leaders to impact medicine's power structure, but that is in the future. It is probably risky for all concerned to accelerate the maturation process too greatly.

I doubt the basis for the contention that increasing the numbers of women physicians will provide an added measure of tenderness and compassion to the profession. Tenderness and compassion are not exclusively qualities of women.

I reject the contention that the increasing number of women in medicine will result in loss of prestige for the profession. If, as I have heard, medicine enjoys less regard as a profession in places such as Russia where women physicians predominate, then I ask, "Which came first?" It is well to remember that until about 20 years ago really choice jobs were rarely available to women. Considering this, it seems more likely to me that the predominance of women physicians in some countries reflects the fact that the field of medicine is not generically attractive to the male. In this country, we do not have such a situation. Rather, we have a long tradition during which physicians have been among the most respected members of society. It is hard to see how anything short of widespread vice, corruption and arrogance within the profession could jeopardize this enviable position.

I look with optimism to the time when women in medicine are no longer tokens, but part, even leaders of the team. I hope that increasing the numbers of women physicians will result in natural corrections of many of the frustrations which women physicians endure today: inadequate call accommodations, lounge space and locker facilities; inequitable pay; and truncated opportunities for advancement. I see nothing to fear from more women in American medicine. It is perfectly clear to me that maleness is not the quality we need to worry about losing. Rather, we should strive to retain that undefinable and indescribable combination of inquiring mind, depth of character and sensitive heart that has made us 93, 93 and 93.

From Josephine E. Newell, M.D., Medical Director of North Carolina Health Benefit Plan

Women physicians face exactly the same problems as do male physicians. We are told that today's medical graduates will face tremendous financial obligations representing educational expenses as well as medical practice "start-up" expenses. This burden will be no easier for females than for males. Many of these young graduates will already have marital responsibilities and children before they enter practice. Certainly, these responsibilities will weigh more heavily on married women physicians than on the majority of their male counterparts. The promise of regular working hours in an HMO set-up would necessarily be tempting to any parent with minor children in the home.

Unfortunately, many North Carolina physicians who favor private practice have closed their eyes to "penetration of the market" by Health Maintenance Organizations. While these physicians have been asleep at the switch, North Carolina's medical world has already been penetrated by three giant corporations — each with an HMO model. North Carolina Blue Cross/Blue Shield assures us that they are being successful in selling their HMO model. HealthAmerica Corporation of North Carolina has run full page ads in all major North Carolina newspapers for the past two months, and states that they are having little difficulty in contracting with both physicians and "business." Now, we are told that the largest and most successful HMO in the nation, Kaiser Permanente, will be estab-

lished in the Research Triangle by July 1, 1984. Since there has, as yet, been no great influx of women physicians in North Carolina, one must assume that there are other factors which led these large corporations to select North Carolina as their marketplace. Their corporate interests are similar to those of other large corporations already located in the Research Triangle. The obvious answer is the rich marketplace for HMOs, provided by the work forces of those other corporations.

In its great wisdom, the Federal Government has created a surplus of physicians — both male and female. Many of these young physicians will find a diminishing market for private practice in their chosen locale, because of the penetration of HMOs and proprietary hospitals with salaried physicians comprising the medical staff. Faced with large debts and families already in place, these young physicians may find guaranteed income and fewer working hours to be extremely attractive — both to men and women.

The anticipated increase in women physicians will not change the practice of medicine. That change will be brought about by the marketplace, political influence, proprietary medicine and entrepreneurial individuals who are not primarily concerned with the quality of medical care provided.

In summary, the women physicians with whom I have been associated during the past thirty years have all been good physicians, who render the highest possible quality of medical care. Most of them have gone the extra mile to shoulder more than their share of the load, despite certain inequities which were to be expected in a predominantly male profession. However, women physicians must not be blamed for the inevitable change in the practice of medicine in North Carolina or the penetration of the market by Health Maintenance Organizations. The new generation of male and female physicians will set the course of medical practice for future years.

From Robert L. Phillips, M.D., a neurosurgeon in Greensboro

Those who are misled into believing Shakespeare's generalization in the *Tempest* — "What's past is prologue," will surely believe that medicine will suffer if the number of women going into this profession continues to escalate. "Their track record is poor . . . they occupy a seat in medical school (that a man should have!), go into practice a few years, then many have a family and kiss medicine good-bye . . . what a waste!" There are still a lot of these "hey-hey" boys around who also believe women have not demonstrated "staying power" and are convinced that only the feminine misfits seek medicine as a career. They freely admit that "occasionally an exceptional one comes along but look at the waste in just getting *that one*." "These women will lead us straight to socialized medicine for it suits their way of life . . . 9 to 5." To our perpetual prophets of doom, all I can say is "gentlemen, change your database!" You can't take a splinter out of someone else's eye if you have a two-by-four in yours. Change is upon us . . . contract medicine is knocking at your door and by the way, women in medicine *will* flourish. With due respect to Shakespeare, not much in the past will help us through this period.

Medicine is, among other things, a social institution. Fortunately, we no longer speak of medical care but instead, health care. This includes help from many people . . . the physician being one part of this complex effort. Those who have felt threatened have used Archie Bunker's technique in trying to "stifle" input from other allied health professionals but fortunately to no avail. What a waste of time and effort, on both sides, when clearly, the tide for comprehensive health care has been in for a long time. The minority struggle has indeed had its casualties, but the Chinese "dripping water" technique has prevailed. Medicine *needs*, as any other social organization does, the input from our women. Many of us have seen organizations change dramatically for the good when women entered the decision making process. They can be innovative, aggressive and often add a new dimension. Think a minute about our male dominated AMA. It has *opposed* almost everything and *proposed* very little . . . the latter usually being a knee-jerk reaction. The HMOs and all the other alphabetical changes are here by necessity. Would it have been different if our medical hierarchy had had feminine input?

Many of us believe women generally are tougher, have more patience, more durability and, perhaps because of the above, have more empathy than their male counterparts. These qualities can only help our health care system. Obviously, some will have the same frailties that the rest of us have and just because one is a female physician, doesn't necessarily mean she will be another Taussig, Morrow or Sharpless . . . but it is my opinion that medicine will continue to be enhanced by her presence. It is long overdue. Conceptually, the women already in medicine and those coming in will probably adapt as well as, if not better than, the men to the HMO since they have been truly the minority group in the social transformation.

Finally, I fully believe that she will, as any good physician will, look beyond the immediate and obvious appearance of things; will cultivate breadth of vision as well as depth of learning; will explore the philosphic and social dimensions of medicine as well as the scientific; and will practice her profession not only with knowledge, judgment and skill, but also with faith, wisdom and love.

From Rose Pully, M.D., a family practitioner in Kinston

In reply to the first question, "Will the increase in number of women doctors change the practice of medicine," my spontaneous remark is: "I certainly hope so for the continuing improvement of the practice of medicine." Yet why would it be expected to change? Are we looking at the female physician to fulfill a role attributed to her because of her gender? Is it true that attributes of nurturing, compassion, people orientation and sensitivity are found solely in women? Of course not. These qualities also reside in the male physician but are downplayed. Despite qualities traditionally attributed to women, the characteristics women display as physicians are formulated by the impact of their professional education, by their adaptation of medical roles and by the organization of their professional life. Women physicians more nearly resemble men physicians in professional attributes than they do other women in the population (Eisenberg: Women as Physicians. J Med

Ed 1983;58:534-541). Women physicians in my early career considered it a compliment to be told "you think like a man professionally." You can imagine the repercussions of such a "compliment" today.

It is of interest that medical schools today are emphasizing the "humanistic attitude or approach in caring for the patient." Even the surgeons are asking for social histories. Since this lack of "caring" on the part of the physician has been a major criticism of the profession and yet, generally, caring is innate in every young medical student, this trait should be constantly nurtured throughout the student and residency years. Thus it may be in full bloom for the years to come.

To look at the past as a measure for the future it is true that women physicians and some of their formal organizations have been more conscious of social issues and a great deal of their energies have been spent in patient caring issues, parent-child interests, and clinics in deprived areas of the world from China to Appalachia. Women physicians have either been happier or accepting of their role in primary care fields, ambulatory and preventive medicine than their male counterparts. Maybe this is accepting realism and adaptation to their life styles. These roles no doubt will be continued by the increasing number of women doctors. Without addressing the biological gender difference specifically it is true that gaps in training and in the ultimate practice of her profession affords the woman with husband and young children some management and psychological problems. This however usually changes the practice of medicine only in the timing sequence. Despite high promise of the increase in male caring responsibilities in home and family and the actual occurrence of this rare happening, I believe that overall acceptance of this idea may be slow in development.

In the past women have largely chosen specialties of pediatrics, psychiatry, general medicine and obstetrics. However with more women physicians their ranks are expected to increase in the surgical subspecialties. With the comfort of their role as medical students in both competitive and non-competitive activities the young female physicians will be more assertive and professionally ambitious than the average physician of thirty years past. How this may change the practice of medicine is uncertain but it should change the system from which the practice originates.

Any exceptional traits to improve patient-physician relationships or change the practice of medicine that are attributed to women physicians need to be discovered and accentuated for both sexes of the medical profession.

In response to the question, "what effect will more women doctors have on the penetration of the market by Health Maintenance Organizations," I have had less experience to reply. As I understand it, the HMO system is a more structured system with regularly scheduled hours, less night call demands than solo practice and some incentives for reduced costs of health care.

In a study by Rosen, Heims, Martindale (Practice plans of today's medical students. J Med Ed 1981;56:57-59) of practice plans of today's medical students the findings indicated that

1. students do not plan to work as hard as predecessors.
2. the future physicians may not have same degree of productivity as is measured today.
3. group practice was planned by 55% of the women and by 48% of the men.
4. gender roles showed no significant difference in their attitudes in practice planning.

All of these have implications for health manpower planning. With the above figures and findings as indicators it could be assumed that the increase in the total number of physicians rather than female physicians would have some effect on the penetration of the market by HMOs. However it cannot be overlooked that the rising cost of health care is an incentive for perpetuation of this system of delivery of health care rather than increasing ranks of women physicians.

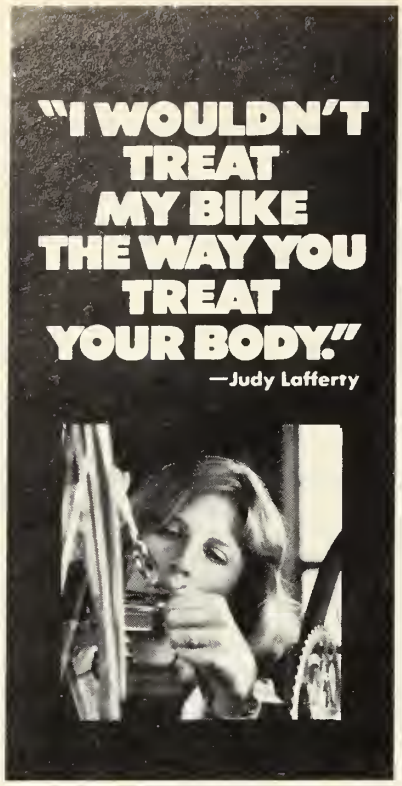
From Margaret C. Swanton, M.D., a pathologist in Clinton

While I was pleased to be asked to participate in your forum related to women physicians, I really have no data to use for a comment. I am a hospital-based physician who has always (30+ years) been on a full-time basis just like my male colleagues. I have no idea how young women physicians are altering the traditional format of practice involving direct patient care. The only one in my community has no choice but private practice, altered since the birth of her baby only by decreased admissions of hospital patients under her care.

From Eldora H. Terrell, M.D., an internist in High Point

It seems unlikely that women doctors who remain single will change the practice of medicine in any significant way. On the other hand, women who choose to combine marriage and children with a medical career soon learn that they cannot serve two masters. They cannot simultaneously be full time mother and full time physician. Their choices are difficult and involve sacrifices. These women doctors can be expected to gravitate toward employment opportunities which offer regular hours and little or no responsibility away from the job. Private practice of medicine does not fit that description. This may not be ideal in terms of career goals but it will be an acceptable compromise. As women have in the past, these will work for less pay in exchange for flexibility of schedule or limitation of hours. Health Maintenance Organizations and other alternatives to private practice can be expected to eagerly tap this rapidly increasing resource of less expensive medical care-givers. This will contribute to their growth and success and to the decline of private practice as we have known it.

• EDITOR'S NOTE: It sounds like women can have whatever impact on medicine that they choose. Decisions women physicians make regarding their time will need to be considered by health man (and woman) power planners and those concerned by the doctor glut.



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This space contributed as a public service

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BRIEF SUMMARY
PRDCARDIA® (nifedipine) CAPSULES For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PRDCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation; 2) angina or coronary artery spasm provoked by ergonovine; or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PRDCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PRDCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PRDCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PRDCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PRDCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients the hypotensive effect of PRDCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and or increased fluid volume requirements have been reported in patients receiving PRDCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PRDCARDIA and a beta blocker, but the possibility that it may occur with PRDCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PRDCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PRDCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PRDCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PRDCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PRDCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PRDCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning PRDCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PRDCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PRDCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PRDCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PRDCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PRDCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PRDCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PRDCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients; transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PRDCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PRDCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphalase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PRDCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PRDCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PRDCARDIA CAPSULE contains 10 mg of nifedipine. PRDCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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Quotes from an unsolicited letter received by Pfizer from an angina patient. While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.

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GENETIC DISEASES

Henry N. Kirkman, M.D.

Ta understand disarders affecting the human papulatian, American physicians and medical students during the first half af this century had ta spend lang haurs learning abaut diseases caused by bacteria and, later, abaut viruses. The need far understanding the infectiaus diseases remains as strang as ever. Relaxation of aur efforts in immunizing children, far example, cauld bring a return af epidemics af paralysis fram poliomyelitis ar af brain damage from whoaping caugh. Ta understand diseases affecting the human papulatian during the latter half af this century, hawever, physicians and medical students are having to learn alsa abaut anather graup af disarders — the genetic or hereditary diseases. Genetic disorders are the reasan far haspitalization af abaut ane faurth af the infants and children wha are in the larger municipal and teaching haspitals af Narth America. Some af these children have canditians that are purely genetic. Examples are muscular dystrophy and hemaphilia. Others have canditians that are partly genetic, such as cleft palate and spina bifida. The present situation is very different fram canditians 50 years aga, when genetic disarders accaunted far anly a small percentage af haspitalized infants and children. Daes this recent trend mean that atomic bamb testing and industrial pallutian have brought new genetic prablems ta the human papulatian? Almast certainly nat. This trend, instead, has accurred because same infectiaus diseases such as tuberculasis, typhoid fever, and diphtheria na langer account far a large prapartian af hospitalized patients. In additian, certain canditians are naw recagnized as being genetic, ar partly genetic, whereas their genetic nature was nat recagnized in earlier decades.

Genetic diseases have impartance because they accaunt far a higher prapartian af illnesses than befare. They alsa have importance because they can be understaad, anticipated, prevented and treated mare readily than befare. We still cannot always tell parents why their infant has a birth defect, but many times the parents can be given a general explanatian af haw the defect accurred and an estimate af the chances that a future child will be similarly affected. Since we have begun ta understand the nature af genetic diseases anly relatively recently, we shauld nat be surprised ta realize that popular misconceptians exist abaut genetic diseases. Same af thase misconceptians are listed in the accampanying table.

Table 1.

Camman Miscanceptians about Genetic Diseases

1. This is the first child in aur family ta have this canditian. Therefare, the canditian is nat likely ta affect future children.
2. The parents af that child must came fram bad genetic stock.
3. My friend, Mrs. X, has an uncle with similar symptams. Therefare, this canditian in aur family must be the same, and inherited the same, as his.
4. We da nat plan ta have further children. Therefare, diagnasis af our affected child is not impartant.
5. I am appased ta sterilizatian and/ar abartian. Therefare, I do nat need genetic caunseling.
6. If I had anly taken better care af myself during pregnancy, my child wauld nat have had Dawn syndrame.

From the Division of Genetics, Deportment of Pediotrics, University of North Corolina School of Medicine, Chopel Hill 27514.

1. Not Genetic?

A potentiolly tragic miscanception is the belief thot an obnormolity is nat genetic ar hereditary if it seems to have accurred in the family for the first time. Achandroplasio is one of the mare common types af dwarfing. Achandroplastic peaple usually have normol intelligence. They hove heods and trunks of normol size, but short extremities. When o child is the first persan in the fomily to be barn with ochondroplosio, there is almast no chonce that o future brather or sister of the affected child will be similarly offected. Yet there will be o 50:50 chance far achondroplosia in each child of the ochondraplastic persan. The opposite is true for disorders belonging ta the lorge group known os autasomal recessive conditions. Of the 1500 ar mare hereditory disorders, one third belong to this group.[1] Examples ore cystic fibrosis, sickle cell disease, ond olbinism. When o child is born with one of the autosomal recessive canditions, there are usually no offected porents, uncles, aunts or causins. Similarly, the chances are very low that the affected child will have on affected offspring in later years. Yet the odds are 25% that a future brother or sister will hove the some problem.

2. Bad Stock?

In many instonces, indeed in most instances, the parents af a genetically abnarmal child do nat hove a greoter number of obnarmol genes or chromosomes thon do the rest of us, even if the porents hove o higher-than-average risk for praducing on offected child. We suspect, for example, that eoch one of us carries three to five genes for severe recessive diseases. If this makes you feel insecure, just remember that we have thousands of genes or hereditary units for contralling our bodily processes — so we can toke comfort in knawing thot we are ot least 99.9% perfect. Whot saves us fram hoving a recessive disease is the duol nature af genetic control. Your blood type is under dual control. It is determined by ane blood type gene fram yaur mother; the other, fram yaur father. Just os the co-pilat can fly and land a jetliner if the pilot becomes ill, our body remains free of recessive disease if only one of the dual genes is defective. If a couple happen by chance ta be both carrying the some type of defective gene for o recessive diseose, however, there would be a 25% chance that their child wauld receive the defective gene from both porents. The situotion then becomes comparable to on oirliner in which neither the pilot nor copilot is functional. The unfortunote thing about the recessive diseases, therefore, is that the parents, by chonce, hoppen ta match up for corrying the same type of defective gene — o coincidence comporoble to o husband ond wife having the same birthdoy.

A similar situotion exists for many of the chramosame abnormalities. Chromosomes are the microscopic particles containing the genes. There are 23 poirs of chromasomes in the cells af narmol peaple. We receive one chromosome af each pair from aur mother, the ather from aur fother. Occasionally, an infant receives either a surplus ar o deficit of chromosamal material in the repraductive cells fram which the infant is conceived. In the case of surplus chramosomal moteriol, there need not be onything wrong with the genes on the extra chramosome. Even if there were, on examination of the chromosomes under the microscope would not usually reveal the obnarmal genes. But the surplus genetic instruction becames o motter of too many cooks spailing the soup. A surplus or deficit of chromasomal material usually results in malfarmations and mentol retardatian. One example of such o chromosamal abnormality is Down syndrame. Children with Down syndrame, which wos formerly called mongolism, are mentally retorded but generolly good-notured and well-behaved children.

For the mast common type af Down syndrome, the porents have normal chromosomes. They shauld not feel, therefore, that their chramosames are any more obnormal than those of other parents in the populotion. If the parents hove normal chromasomes, haw then did they came ta hove o child with the extra chromosome? As each cell af the body is obout to divide, the cell has o difficult task af duplicating the chromosomes and parcelling them equolly between the resulting cells. This is a complicoted process with on intrinsic rate of error. As might be imagined, o small percentage of the cells in our body will end up with one tao mony or one too few chromosomes. This is olso true of our reproductive cells. Eoch of us hos a small fraction af reproductive cells with an obnormol number of chromosomes. The child with Down syndrome wos unfortunate enough to have been conceived from such o repraductive cell. By the luck of the drow, your awn child could have been conceived with an extro chromasome. One illustration of how reodily this occurs omong chromosomally normol porents is the finding that neorly half of all miscorriages represent chromasomolly abnormol embryos. If we assume thot some 20% of canceptians end up as miscarriages, then we realize that obout 10% of all conceptions result in embryos with an obnormal number of chromosomes. We should not think thot parents af geneticolly abnormol children alwoys have normal genes and chromosomes, but we should remember thot for same of the more common types of genetic problems the genes and chromosomes of the parents are os normal os those of the average person.

Nar shauld we suspect thot such porents come from some genetically blighted ethnic group if the parents happen to belong to on ethnic group different from our own. To be sure, certain genetic diseases ore concentrated in specific ethnic groups. Sickle cell diseose occurs largely in blocks, Toy-Sachs diseose in people of Jewish ancestry, and hemaglobin E disease in Orientols. If you are tempted ta take comfort in the foct thot you do

not belong to ony of those groups, ond thot yaur ancestors lived in Western Eurape, then you might reflect on the fact that your ethnic group is prone ta cystic fibrosis, phenylketonurio (PKU) and spina bifido. Nome your ethnic bockground ond the medical geneticist will tell you which genetic disorders ore porticulorly prevolent in your graup. Mareover, certoin genetic problems, such os chromosome abnormalities, seem to be about equolly common in oll ethnic groups thot have been studied. While walking or driving, I hove seen people with Down syndrame in such diverse ploces as Solisbury, England; Assisi, Italy; Baane, North Corolina; and Kunming, Chino.

3. The Error of Self-diagnosis

Physicians encourage odults to look for early signs of concer in themselves: women to exomine their own breosts for lumps, men and women to notice if blood is present in stools. But physicians do not wont their potients to ossume, on their own, thot the problem does or does not represent cancer. The potients should report their abservotions to their physicions promptly. Similarly, adults should be olert to the possibility of o genetic disease in their own fomily ond express their concern to their physicion, but nat ottempt to make the diognosis themselves. With both concer ond genetic diseose, keeping quiet con hove unfortunote consequences. The consequences con be unfortunote either woy. A mon might commit suicide, thinking thot he is ot risk for developing Huntington's diseose, which killed his grondfother ond apporently killed his mother. Yet reoding of the medical records and autapsy results on his mother might reveal thot she octuolly died of olcoholism, nat Huntington's diseose. Or the opposite might be true. He could mistakenly ossume that he and his future children ore not at risk because he thought his mother died of alcoholism.

One of the more difficult tosks preceding genetic counseling is distinguishing the condition fram ones thot may resemble it very closely but have an entirely different mode af inheritance. In generol, the diagnosis must be made even mare occurotely far purposes of genetic counseling than for purposes of routine medical or surgical monogement ond treotment. An exomple is deofness at birth. Such cangenitol deofness might be the result of the mother's having had Germon meosles during pregnancy, in which cose there would be na increased risk for deofness in future children. Or the deafness might represent an autosomal recessive type of deafness, in which case the risk would be 25%. Yet the day-to-day management of the two types of deofness might be essentially the same. An even more impressive example of the need for distinguishing between subtypes is Down syndrome. With the most common type of Down syndrome, the porents run a 2% risk that a future brother or sister of the offected child will also have Down syndrome. For o less common form of Down syndrome, the risk is 15%; ond for o fortunotely rore form af Down syndrome, the risk is 100%. The risk con be 2%, 15% or 100%. Yet there is no woy by which o physician, even o medical geneticist, can distinguish one type of Down syndrome from the other by physicol exominotion of the affected child. The distinction must be made by exomination of the chromosomes in a blood sample from the potient with Down syndrome. If the chromosome exomination (koryotype) reveals thot the Down syndrome is of the trisomy 21 type, as is usuolly the cose, then no examination of the chromosomes of the parents or other relatives is necessary. It is known that this type of Down syndrome hos no strong tendency to occur in the offspring of normol oppeoring relotives. If the affected child hos tronslocotion Down syndrome, however, examinotion of the chramosomes of the porents and possibly other relatives will reveal exoctly which relative, if any, is liable to have on affected child. Antenatol (prenotol) diognosis would be one of the options ovailoble to that relative.

4. Diagnosis not important?

This complexity with Down syndrome, incidentolly, is the primory reoson why medicol geneticists believe that oll patients with Down syndrame should hove their chromosomes examined and, equally importontly, that porents, uncles, and aunts should be told whether ar not this is the type of Down syndrome that tends to run in families. Parents af the persan with Down syndrome sometimes tragically refuse to allow blaod samples to be drawn for chromosome analysis on their son or

WHY SHOULD WE BE CONCERNED?

Eoch yeor in the United Stotes obout 250,000 infonts ore born with birth defects. It is estimoted thot of the 84,000 children born onnuolly in North Carolino, more thon 4,000 will be offlicted with birth defects ond other genetic problems. The following toble lists the number of North Corolino children born with some genetic conditions.

Down Syndrome	128
Cleft lip or cleft lip ond polate	114
Neural Tube Defects (Spino Bifido)	120
Hemoglobinopothies (Sickle Cell, etc.)	185
Cystic Fibrosis	35
Phenylketonuria (PKU)	4
Hypothyroidism	12
Mentol Retordotion	2512

An estimoted 352,000 North Corolinions hove o hondicopping genetic condition. Birth defects constitute the third most common couse of deoth up to oge 14. It is estimoted thot 35% of all pediatric hospitol odmissions ond 40% of infont deaths ore due to genetic conditions.

doughter with Down syndrome. They might refuse such examinotion becouse they believe: (a) the diognosis of Down syndrome is certoin, (b) they do nat plan to hove ony more children, (c) they consider the problem to be a personal motter of no concern to others, or (d) "Johnny hos already suffered enaugh." In fact, chromosome onolysis is not done just to tell the porents whether or not the child hos Down syndrame or even whether ar not future brothers ond sisters will hove the same condition. It is done to tell whether or not future cousins, nephews, ond nieces will hove the same problem.

MEDICAL GENETICS CENTERS

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Genetic Counseling Progrom
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306 Biologicol Sciences Bldg. 220H
Chopel Hill, N.C. 27514
Diognostic Evoluotions &
Genetic Counseling 919/966-4202
Prenotol Diognosis 919/966-1447

CHARLOTTE
Genetic Counseling Progrom
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Medicol Center
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Charlotte, N.C. 28234
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Deportment of Pediotrics
School of Medicine
Eost Carolino University
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WINSTON-SALEM
Genetic Counseling Program
Deportment of Pediatrics
Bowman Gray School of Medicine
300 Howthorne Rood
Winston-Solem, N.C. 27103
919/748-4328

The telephones of the Genetic Counseling Program in Chapel Hill ring from time to time with o call from an abstetrician or family physicion wanting to know the diognosis of a Narth Carolino child evaluoted in our laboratory or clinic. The physicion is toking core of the child's ount or older sister, who lives in Oregon or Texos, ond the physician wonts to know if this pregnant aunt or sister is at risk for hoving o similorly affected child. Such telephone calls, which are occurring with increosing frequency, also justify the encouroging af porents to permit autopsy ond full diagnostic evaluation of infonts who die with molformotions or metabolic abnormalities. In the course of normol grief over losing o newborn infont, porents may refuse to ollow such evoluotions, yet often the porents will return to their physician or hospitol in subsequent months or years wonting to know the couse of death, whether the abnormality is likely to occur ogoin ond whether ontenatol diognosis or eorly treotment might prevent o similor outcame. Even when the parents plon to have no more children, the normol aunts, uncles, ond older siblings moy osk the same question. Sessions on genetics, birth defects, ond chromosomes in high school are cousing young odults to ask mony more questions about such motters thon did yaung odults of eorlier decades.

5. Non-directive Nature of Counseling

Most medicol geneticists do not advacote that all genetic counseling be done ot genetic clinics. The genetic disorders ore simply too cammon to allow this, regordless of whether or not it is desiroble. Consequently, the procticing physicion will be providing this service in certoin instonces, especially when he or she hos the time ond troining to distinguish the condition from genetically distinct abnormalities that clasely resemble the condition. In the process of exploining the noture of genetic counseling to medicol students ond physicians, medicol geneticists point out that genetic counseling should be non-directive. In contrast to monaging a patient with appendicitis or with eorly signs of meningitis, we do not tell potients whot to do. Choosing omong the vorious options thot moy be possible — hoving odditionol children, ovoiding childbearing, ortificial inseminotion (for outosomol recessive diseases), ontenatol diagnosis (if passible) ond selective obortion, eorly treotment, ond odoption — is a personal motter. The choice is best mode by the couple, who will after oll be the ones who must live with their decision. This is porticulorly oppropriote since one can obtain differences of opinion even omong medicol geneticists os to which choice is best in o porticulor instonce. It is importont thot the couple moke the decision thot they will feel most comfortable living with. The overoge couple, however, will most certoinly need informotion obout how severe or how mild the disease is. An intelligent decision connot be mode without the cauple's having o reolistic understonding of the emotional ond finoncial burden of the disease on the one hond, or the ease with which it con be treoted on the ather hand. Most importont is thot couples not ovoid genetic counseling if they ore opposed to sterilizotion or obortion. If they hove such oppositions, their options ore reduced ond their understanding of other options becomes even more importont.

6. The Positive Side

All is not doom and gloom in genetic counseling clinics. Neorly holf of the couples coming ta Chapel Hill leorn thot their chonces of hoving o normal child are even better thon they thought. Those who provide genetic counseling have the pleosure of being able to dispel inoppropriote feelings of guilt ond blome. Mothers of chromosomolly abnormal children, for example, often secretly blome themselves far causing the birth defects of their child. The mother

believes thot the birth defect wos caused by something that she did during the pregnoncy — gaing on o long trip, taking a heodoche powder. The medicol geneticist is oble to point aut thot the chromosomol obnormality wos determined at the moment af conception. It wos not coused by onything which the mother did or did not do during pregnoncy. Mothers-in-law, suspecting that the recessive gene must hove been one of those "bod tendencies" coming from the ather side of the fomily, can be reminded thot the obnormol genes come from bath sides of the fomily and thot they were probably possed in hidden form from one generotion to the next for mony generotions. Studies of certoin genetic conditions are reveoling the extent to which the bod consequences of the condition con be prevented by eorly diognosis ond treotment. Diognosing offected potients in infoncy ond plocing them an special treotment con prevent the mental retardation of PKU, the stunting of growth ond bowing of legs of hereditary rickets (a condition porticulorly common in North Corolina), and the blindness of goloctosemio. A blood test on pregnont women, ot 16-18 weeks in the pregnoncy, will detect obout 80-90% of the coses of anencephaly (apen skull ond obsence of brain develapment) or severe spino bifida. Although those apposed to obortion may abject to the availability af this test, they shauld know that the results af the test strongly determine haw ond where the waman shauld deliver the infant, even if she chaases nat ta have an abartion. Moreaver, the intraduction af this test in the British Isles, and the simultaneaus studies af cauples having infants with these defects af skull and spine, resulted in a surprising finding. Such mathers seem ta be much less prane ta have anather affected infant if the mather begins toking a prenatal vitamin tablet, cantoining falic acid, *befare* the next pregnancy. Spina bifida and anencephaly are relatively camman in Ireland, Scotland, ond England. Perhops the accurrence of these birth defects in white people af North Corolino is due in port to the Irish, Scottish, ond English ancestry of mony of the peaple af Narth Carolina. Whether this vitomin opprooch will prevent onencepholy ond spino bifido in the United Stotes remoins to be determined, but this hoppy development in the British Isles serves to illustrote how much the approoch to genetic conditions can differ from the grim features that ane might suspect.

In oddition, the field of medicol genetics is not becaming just onother super-specialty in medicine. It is farcing eoch physicion to became o bit more of a generolist. The dislocoted lens of the eye, which the ophtholmalagist sees, moy represent a condition known os Morfon syndrome, which requires the ottention of fomily physicions and cordiolagists. The urologist who diognases o potient os hoving kidney stones due to cystinurio is obliged to remember that sisters and brothers con olso be offected with this condition, for which prevention ond medical treotment of the stones ore passible. Finolly, odvonces in understonding genetic diseoses enoble fomily physicions ta live up to their nomesoke. The development of the field of medicol genetics, therefore, is o trend thot will cause o broodening ond interoction of the vorious fields of medicine in a monner that same af us find ta be most welcame.

Medical Genetics in North Carolina

When giving out-af-state lectures abaut medical genetic prablems in Narth Caralina, I am often appraached afterword by physicians wha ask haw Narth Caralino came ta have mare genetic prablems than ather states. The answer, of caurse, is that Narth Caralina probably daes nat have mare genetic prablems thon ather states. Thase physicians are simply unaware af the extent to which genetic prablems are present in their awn state. Few of us reolize that there is a notianal oward far teoching and reseorch in humon genetics. This oword, given periadicolly ot annuol meetings of the Americon Society of Humon Genetics, is colled the Williom Allon Aword.[2] It is named ofter a North Corolino physician, Williom Allon (1881-1943), who corried out some af the eorliest observotions on the genetic noture of certoin humon diseoses. During the 1960s, North Coralino wos criticized for not odopting o bocteriol method for checking newborn infonts for the condition known os phenylketonurio (PKU). Newborn infonts in North Corolino ond most ather stotes ore tested for this conditian routinely. If the offected infont is diognosed ond storted on o speciol diet soon ofter birth, the infant is spored from developing severe mentol retordotian. Rother thon use the bocteriol method, heolth afficiols of North Corolino odopted[3] on outomoted fluorometric method de-

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velaped by twa North Caralina physicians, Dr. Jahn Hill and Dr. Gearge Summer. This methad is praving ta be mare accurate than the bacterial methad. Health afficials in certain states, where North Caralina was criticized, are beginning ta switch ta the autamated fluarametric methad.

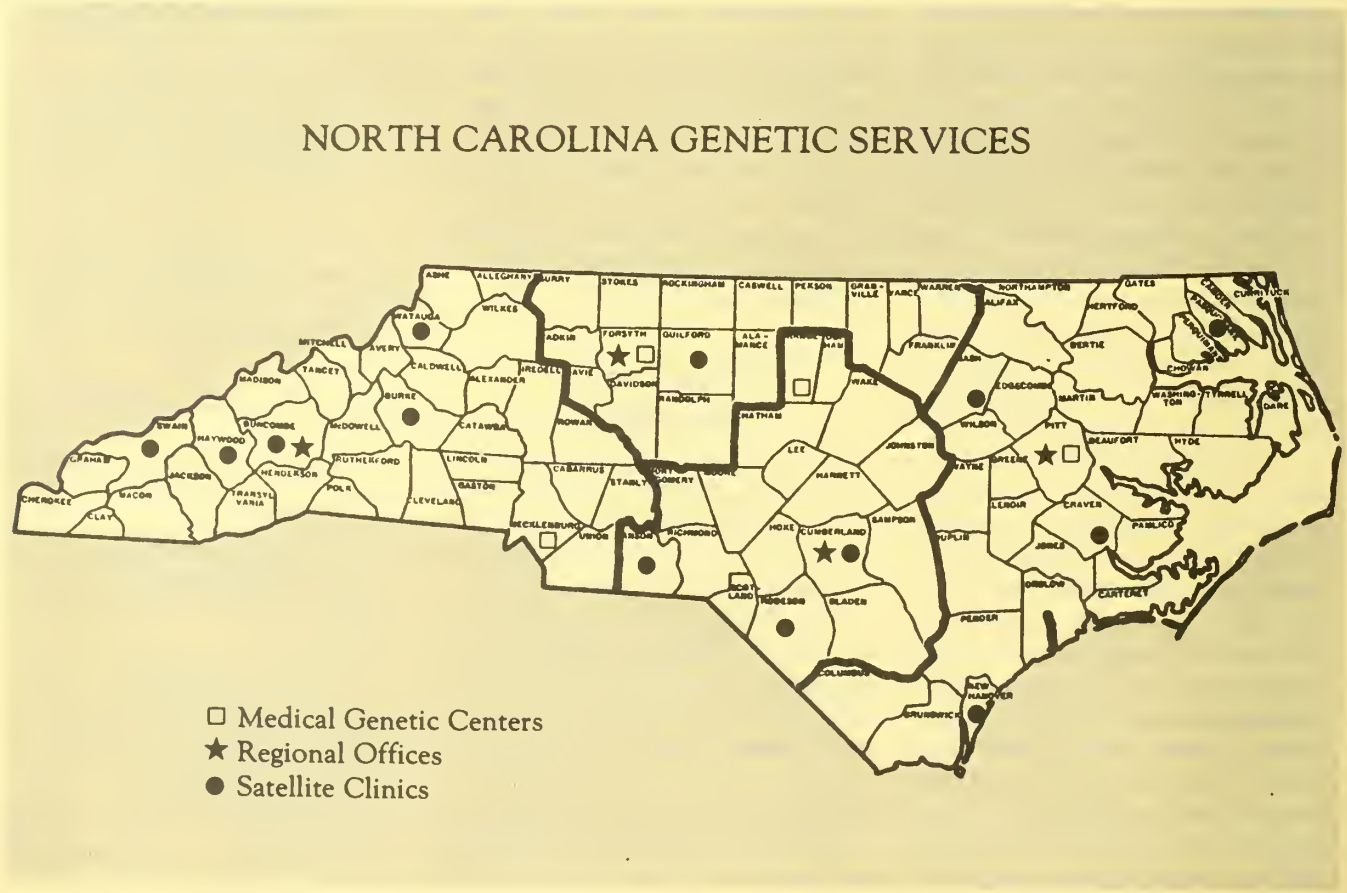
Mareaver, an a per capita basis, North Caralina is unusually well represented in the directary af peaple wha have successfully passed a baard certificatian examinatian that was recently given by the Natianal Baard af Medical Examiners and by the new American Baard af Medical Genetics. With the inclusian af peaple wha have campleted their training and have gane ta ather medical centers, the directary cantains an impressive number af names af peaple fram North Caralina and especially fram Chapel Hill. North Caralina was ane af the first states ta pravide state funds far genetic clinics, including clinics where genetic counseling wauld be available ta peaple least able ta affard the counseling, such as yaung cauples whase savings were depleted by a lengthy haspitalizatian af their first child. March af Dimes funds and State funds alsa pravided far clinics in ather North Caralina cities ta which physicians fram the medical schaal in Chapel Hill cauld fly ta assist in the diagnasis and counseling af families with genetic disarders. Such aut-af-tawn clinics are being held alsa by the staff af Bawman Gray Medical Schaal. One ar mare peaple, baard certified in medical genetics, can be faund an the staff af Charlatte Memarial Haspital and at each af the faur medical schaals in North Caralina.

Additional Reading

Yau will find mare details an the subject af genetic diseases in *The Genetic Cannectian. Haw ta Pratect Yaur Family Against Hereditary Disease*, by David Hendin and Jaan Marks.[4] An excellent 22-page pamphlet, *Genetic Counseling*, is available thraugh the March af Dimes Birth Defects Faundatian in Raleigh (Mr. Jack McGee, P.O. Bax 10691, Raleigh 27605) ar thraugh yaur lacal March af Dimes Office. In additian, a shart pamphlet, *All Abaut Genetic Services*, can be abtained fram the Divisian af Health Services, Department af Human Resaurces, P.O. Bax 2091, Raleigh 27602.

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Rocky Mountain Spotted Fever

Claude S. Burton, M.D., Peter W. Heald, M.D., and J. Lamar Callaway, M.D.

This is one disease that could have been called North Carolina Tick Typhus had it not been first discovered in the Rocky Mountains of Montana. North Carolina leads the world in cases of Rocky Mountain Spotted Fever (RMSF) and tragic fatalities occur often. The number one cause of death is delay in diagnosis. Though we don't need the notoriety of such a frequently tragic disease, too little attention has been given to informing our citizens about RMSF.

A bacterium known as rickettsia rickettsii (named for Dr. Howard T. Ricketts, the discoverer of the organism) is responsible for the disease. The bacteria live in the tick and are excreted in tick droppings and saliva. Man becomes infected when bitten by an infected tick and by direct contact with the rickettsiae through openings in the skin (i.e., when removing ticks). Human infection has also occurred by aerosol transmission to laboratory workers studying the disease. Fortunately not all ticks carry RMSF. A study of Piedmont, N.C. ticks found that less than 1 in every 1000 ticks were carrying the bacteria. Since ticks often crawl about for a few hours before biting, one may remove the pest before inoculation occurs. Therefore, a fear of ticks is unwarranted and the threat of RMSF shouldn't keep us from enjoying the woodlands. Not all ticks that harbor bacteria are equally virulent. For reasons that are not clear, exposure to a blood meal renders the bacteria much more likely to produce serious disease. The incubation period varies from 3 to 14 days. The shorter the incubation the more serious the disease.

Doctors and patients invest too much importance in a history of tick exposure when considering whether or not they are dealing with RMSF. Never be misled by the lack of a tick history. Half of the patients with RMSF deny tick exposure. Ticks are often found in most unlikely places including nursing homes, department stores and even hospitals. Virtually everyone reading this article has been exposed. Enough about ticks. A patient recently admitted to our hospital after accidental thumb amputation developed a rash several days after hospitalization. What was thought to be a drug related rash proved an biopsy to be RMSF! Though the illness was most likely in the incubation phase when the patient was admitted to the hospital, this case emphasizes the need to be constantly on the alert, even in unlikely circumstances. Cases have even been reported from blood transfusion.

The early symptoms of RMSF are common to many diseases. Fever is the only consistent finding and may be masked by aspirin or Tylenol. The rash is not present in all cases and may be so obscure that a magnifying glass is necessary to identify its presence. The rash is of enormous benefit if present and biopsy of the rash often establishes the diagnosis. In certain high risk groups (over 50, blacks) the rash is often a late sign associated with a guarded prognosis. In view of the frequently obscure and occasionally absent rash, neither patients nor doctors should rely on this criterion. Frequently noted symptoms include headache, nausea, vomiting, and cramps. However, the list of reported symptoms is virtually endless. Common misdiagnoses are "flu" and "viral syndrome."

The diagnosis of RMSF should be carefully considered in anyone with fever during the tick season. If there is any doubt, doctors should err on the side of overtreatment. The drugs used to treat the disease have rare side effects whereas missing a case of RMSF may prove fatal to the patient. Only tetracycline and chloramphenicol are effective against RMSF. Tetracycline is the drug of choice for adults but stains the teeth of children. Chloramphenicol doesn't stain the teeth but is an very rare occasion associated with fatal suppression of the bone marrow. For this reason a five day course of tetracycline is suggested for a febrile illness in children lasting more than two days. No fatalities occur in animals with RMSF treated with tetracycline early in their illness. We are often asked, "Why not take one of these drugs prophylactically if you are bitten by a tick?" Interestingly, such an approach doesn't work. Until the patient's defense mechanisms mount to fight the infection, the bacteria proliferate, despite antibiotics.

During the tick season check yourself, your children, and your pets for ticks. Fat fertile female ticks may drop from your pet to lay thousands of eggs. Since infected ticks pass the organism to their offspring, a house may become infested with infective ticks. There are several reports of multiple members of a family developing RMSF. When removing ticks, prevent self-inoculation by using tweezers, paper napkins, etc. Avoid areas of heavy infestation. Drag a cloth around an area before picnicking to check the tick population. If you find ticks in great numbers, move.

Most importantly, seek medical advice for any fever during the tick season and ask specifically about RMSF. No one need ever die of this disease.





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Nancy Ray has multiple sclerosis.

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MS can be mild. Or it can be severe. Once you've got it, you've got it for life. Most days, Nancy Ray can get around with a walker. With a lot of time and effort, she can even prepare meals for her family. Some people with MS aren't that fortunate.

The National Multiple Sclerosis Society is helping people with MS live with MS. And funding research for a cure, all over the world. We can do it, but only with your help.

Please give generously. It's tough enough to be a mother without MS.

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Adjunct in short-term treatment of pain accompanied by tension and or anxiety in patients with musculoskeletal disease. Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone. Effectiveness in long-term use, i.e. over 4 months, has not been assessed by systematic clinical studies. Physicians should periodically reassess usefulness of drug for individual patients.

CONTRAINDICATIONS:
ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria, allergic or idiosyncratic reactions to meprobamate or related compounds, e.g. carisoprodol, mebutamate, or carbromal.

WARNINGS:
ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE: DRUG DEPENDENCE: Physical and psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually, greater than recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms, e.g. anxiety, anorexia, or insomnia or withdrawal reactions, e.g., vomiting, ataxia, tremors, muscle twitching, contusional states, hallucinosis, and, rarely, convulsive seizures. Such seizures are more likely in persons with CNS damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation, symptoms usually cease within next 12- to 48-hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks, rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e.g., driving or operating machinery.

ADDITIVE EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION:
An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug.

Meprobamate passes the placental barrier, it is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS:
ASPIRIN: Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excrated by the kidney; to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should bo prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS:
ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS: Drowsiness, ataxia, dizziness, slurred speech, haadache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity.

GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transiant ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Mildar reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalizad or confined to the groin. Other reactions include leukopenia, acuta nonthrombocytopenic purpura, petachiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, lever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate/mebutamate and meprobamate/carbromal. Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angionaurotic edema, bronchospasm, oliguria, and snuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC"): Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms.

DOSAGE AND ADMINISTRATION:
Usual dose is one or two tablets, 3 to 4 timas daily as needed for relief of pain when tansion or anxiety is present. Not recommendad for patiants 12 years of age and under.

OVERDOSAGE:
Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should ba removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may raduce absorption of both aspirin and meprobamate. Aspirin overdosage produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include managament of hyperthermia, specific parenteral electrolyte therapy for katoacidosis and dehydration, watching for avidence of hemorrhagic manifastations due to hypoprothrombinamia which, if it occurs, usually requires whole-blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lathargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been latal. The following data, reported in the literature and from other sources, are not expected to correlate with aach case (considering factors such as individual susceptibility and langth of time from ingestion to treatment), but represent usual rangas reported. Acuta simple ovardose (maprobamate alona): Death has baen reported with ingestion of as little as 12 grams maprobamate and survival with as much as 40 grams.

BLOOD LEVELS:
0.5-2.0 mg percent represents usual blood-level range of meprobamate after therapautic doses. The level may occasionally ba as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdosage, such as stupor or light coma.

10-20 mg percent usually corresponds to deeper coma, requiring mora intansiva treatment. Some latalities occur.

At levels greatar than 20 mg percent, more latalities than survivals can be expected.

Acute combined overdose (meprobamate with othar psychotropic drugs or alcohol): Since affects can be additiva, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue laval) cannot be used as a prognostic indicator.

In cases of excessiva doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal lavals. Any drug remaining in stomach should be removed and symptomatic treatmant given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and preasor agents should be administarad cautiously as indicated. Diuresis, osmotic (mannitol) diuresis, paritoneal dialysis, and hemodialysis have been usad succaasfully in removing both aspirin and maprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is nacessary, and caution should be taken to avoid overhydration. Relapse and daath, after initial recovary, have bean attributed to incomplete gastric emptying and delayed absorption.

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Beware The Xanthines Bearing Gifts: Theophylline Overdose

Ronald B. Mack, M.D.

ONE of my favorite stories involves the Trojan Horse, as told in Virgil's *Aeneid*. One of the many lessons it should teach us, as health care professionals, is that nothing is ever exactly as it seems; you must be skeptical enough to ask lots of questions before accepting only what appears to be obvious.

The Ancient Greeks talked a lot about *hubris* — overwhelming pride or presumption — it often led to the tragic fall of a hero. After fighting the Trojans for 10 years, the Greeks decided to leave Troy and return home. In their place they built a very large wooden horse filled with warriors which they alleged was an offering to the goddess Minerva to ensure their safe passage home. The Trojans, suffering from acute hubris, decided to take the horse into the city — they were so proud of themselves after the Greeks retreated. There was at least one hero in this tragic story and his name was Laocoon. This fellow was a priest of Apollo's Temple and he tried to warn his countrymen against the dangers of this gigantic wooden beast whose insides he considered potentially bad news indeed. Nobody listened to this poor fellow and he and his two young sons were strangled and crushed to death by two horrible sea serpents who rose from the waves and did them in. The rest is history as they say. Let me therefore warn you about the dangers of theophylline. I do this without hubris and with a good supply of sea serpent antivenom on hand.

Theophylline is a drug in very common use for treating acute and chronic pulmonary problems. If you take care of sick children and/or sick adults the chances are you use a fair amount of this product. It's hard to pick up a medical journal these days that doesn't have a new article on theophylline therapy or an advertisement on a new theophylline preparation. You must realize that theophylline, as useful as it may be, has a very narrow therapeutic range and overdosage can be a tremendous problem for the patient and the clinician.

Fortunately a lot is known about this drug in terms of pharmacokinetics, and blood levels are quite readily attainable. Most of the following data does not apply to the slow release preparations. Theophylline is a methylxanthine which is quite rapidly and efficiently absorbed from the GI tract when taken per os, with peak blood levels occurring within 2 hours of ingestion. About ½ to ⅔s of theophylline is bound to protein. The volume of distribution (V_D) is 0.5 L/kg and au courant readers will immediately see this drug's potential for extracorporeal removal in case of serious overdose. As with many drugs, age of the patient is a prominent feature in this drug's metabolism. Thus, clearance of this medication progressively increases and the half life (T½) decreases from birth to about 9 months of age. Maximal clearance is thought to be achieved during the ages 1 to 9 years. After 9-10 years of age clearance decreases into adolescence and tends to stabilize in the mid-teen years. At therapeutic levels the T½ also varies with age, going from 20 hours ± in the full-term newborn to 6-7 hours in the first 6 months of life to 3.5 to 5 hours from 1 to 18 years and finally 4.5-5 hours for adults. About 95% of theophylline is metabolized by the liver following first order kinetics (elimination is directly proportional to the amount of drug remaining) at therapeutic levels and first order and zero order kinetics (zero order kinetics = elimination that occurs at a fixed ratc regardless of the amount of drug remaining) in overdose situations. To put it more succinctly, the T½ varies quite a lot depending on age group, other diseases or other drugs on board at the same time, etc. The T½ in normal and asthmatic adults has a mean of approximately 5.8 hours and in children, a mean half life of about 3.69 hours.

Theophylline is really a neat drug in terms of its action. We know that it relaxes bronchial smooth muscle (of course that's why you give the drug. What did you think it was, an aphrodisiac?). Theophylline is involved with cyclic AMP (this is not a gossip item, it's the truth). Cyclic AMP has to do with the release or inhibition of "mediators" that can affect bronchial smooth muscle, among other things. If you can increase the cyclic AMP you can inhibit these mediators and that's good. Cyclic AMP is degraded by the enzyme phosphodiesterase and theophylline inhibits this enzyme and thus cyclic AMP increases and that's really good if you have asthma. This drug may also inhibit some *prostaglandin* activity and thereby lessen contraction of bronchial smooth muscle. Some authors believe that the drug may enhance catecholamine activity. No matter how it works, it can dramatically change the life of a stricken asthmatic if given in the correct dose for the patient.

In the event of overdose, either due to "therapeutic misadventure" or accidental ingestion or even purposeful ingestion, the consequences can be awesome. The evil effects can range from a little headache and bellyache to coma and seizures and even death. We are all aware by now that you should aim for a therapeutic blood level of *10-20 μg/ml*. Toxicity appears to be related to the serum concentration, e.g., *mild* toxicity can be seen at a serum level of *20-40 μg/ml* and *severe* toxicity at *40-80 μg/ml*. However, bear in mind that mild symptoms can occur even at therapeutic theophylline levels and children seem to be more

tolerant to toxic levels of this drug. The *CNS, GI,* and *cardiovascular* systems are the main target organs in a theophylline overdose.

Before we begin to think about the specific effects that occur in a theophylline overdose some thought should be given to the *physiological* effects of theophylline as opposed to the *pathophysiological* effects. The "Trojan Horse" phenomenon might be seen here because knowing the physiological effects of the xanthines can help you to predict the powerful clinical results resulting from overdose. Let's try to "empty the horse" to see what the extent of damage could be when the drug is used unwisely. (Is this analogy too arcane? Did I lose many of you? I'm sorry!!) The xanthines, especially drugs like theophylline, can stimulate the cortex and medulla and have secondary effects as a result of such CNS stimulation on skeletal muscle, cardiovascular, respiratory and gastrointestinal systems. As a primary action on the *cardiovascular* system there is an increased rate (chronotropic) and force (inotropic) of cardiac contractions. The gastrointestinal tract responds by increasing gastric acid and pepsin secretion. There is increased renal blood and diuresis with theophylline use but the good news is that this drug relaxes bronchial smooth muscle and increases ventilation and that's great because that's probably the reason you used the stuff in the first place. Theophylline produces many other effects that you may or may not want your patient to endure such as a decrease in potassium and an increase in both lipolysis and glycogenolysis and catecholamine release.

In theophylline overdose in a mild case (20-40 μg/ml ±) the patient may only complain of headache and insomnia plus palpitations, anorexia, nausea, vomiting, and abdominal pain and exhibit tremors and tachycardia. In more advanced overdose situations the patient is confused, maniacal or stuporous and has more vomiting and diarrhea and can be quite tachypneic. In severe theophylline overdose (40-80 μg/ml) we are talking big trouble. It is even more frightening to face the prospect that the milder effects of overdose may not necessarily precede the life threatening features of coma, seizures, GI bleeding, hyperthermia, cardiac arrhythmias and shock in about one-half of the cases. Seizures seem to be more common when the serum theophylline level rises above 50 μg/ml. Although generalized seizures are the more typical cerebral dysrhythmic response, focal seizures may occur. Tachycardia is thought to be the most universal sign of theophylline poisoning. Cardiovascular collapse is not common with serum concentrations below 50 μg/ml.

Knowing what we now have learned about theophylline overdose, the work-up becomes somewhat easier to figure out and should include a theophylline level, an EKG, a hemoglobin and crit, serum potassium level, arterial blood gases, chest x-ray and an examination of gastric contents and stool for blood. For the best results, using current technology, measure serum theophylline by high pressure liquid chromatography as it is the *most accurate* so far. In an acute overdose situation, *take more than one level* before you decide that the overdose was or was not significant and this is especially true in suspected overdose from slow release theophylline preparations. Serial theophylline levels will help you to determine the elimination rate as well, which could help you determine how long your patient was subjected to a toxic level. Let me emphasize again that with very large overdoses or the ingestion of sustained release theophylline preparations at least two specimens, 4 hours apart, should be obtained for serum theophylline concentration.

The treatment of theophylline overdose is not as futile as with some other toxins and some new therapeutic modalities make efficient therapy potentially available to even some of the smaller hospitals. You have to empty the patient's stomach — not much argument here — by either the use of ipecac or gastric lavage depending on the patient's level of consciousness. Gastric contamination should be performed almost regardless of the probable ingestion time. The administration of activated charcoal is of paramount importance and should be followed by a saline cathartic. One of the newest suggested methods to "deactivate" the ingested theophylline is to administer repeated doses of activated charcoal. It is believed that this charcoal not only stops further absorption of the theophylline that remains in the GI tract but apparently absorbs theophylline from the bloodstream across the capillary bed of the small intestine. This, in my opinion, is a very exciting breakthrough as it is relatively benign, fairly easy to do and obviates the need for specialized equipment. Theophylline is very well absorbed by activated charcoal. The activated charcoal should be administered about every 4 to 6 hours until the serum theophylline level decreases below 40-60 μg/ml. This method should decrease the T½. It is probably a good idea to give a saline cathartic with each dose of charcoal because if you don't the patient might have great difficulty "passing" the charcoal and will end up with material that is only suitable for use as an outdoor cooking material for barbecues.

Seizures, more so in adults than in children, can be a real headache to the "treater" as well as the treated. They seem to be more common with serum theophylline levels above 50 μg/ml and can be terminated with parenteral diazepam or barbiturates or phenytoin. *Hypotension* not responding to intravenous fluids can be combatted with pressor agents, e.g., norepinephrine or dopamine. You can give propranolol or digoxin for *supraventricular rhythm* disturbances and lidocaine or propranol or phenytoin for *ventricular arrhythmias.* Pronounced *GI bleeding* should be treated in the conventional manner with IV fluids and blood. Unfortunately, fluid diuresis is not very effective in removing theophylline from the body. Pay careful attention to potassium levels and needs.

In very severe cases of theophylline overdose there is, fortunately, a possible life-saving therapeutic modality — extracorporeal removal. That is to say, you can remove theophylline via dialysis (either peritoneal or hemo) or hemoperfusion. There is no question in my mind, at least with current knowledge, that hemoperfusion is the way to go. Theophylline lends itself nicely to this procedure; the volume of distribution is only 0.5 L/kg. Charcoal or resin hemoperfusion can remove considerably more theophylline than the other currently used extracorporeal methods. There are probably no absolute levels of theophylline that mandate use of hemoperfusion but intractable cases of arrhythmia or coma or hypotension or seizure should be

considered as candidates. Some authors suggest hemoperfusion at levels of 100 μg/ml for acute overdose and 60-80 μg/ml for the slow release theophylline preparations. It has recently been recommended that extracorporeal measures should be used in pediatric patients who fail to respond to more conservative methods or whose serum concentrations exceed 80-100 μg/ml. A new experimental regimen, only tried in a small number of patients so far, suggests that propranolol may be the "antagonist" of choice and *could* be considered in those patients who are "too sick" to be hemoperfused.

I must leave quickly now, I've warned you and I now see two giant sea serpents being brought into our clinic in a Winn-Dixie shopping bag and frankly I am scared. Quickly nurse, get me my anti-hubris pills and sea serpent anti-venom.

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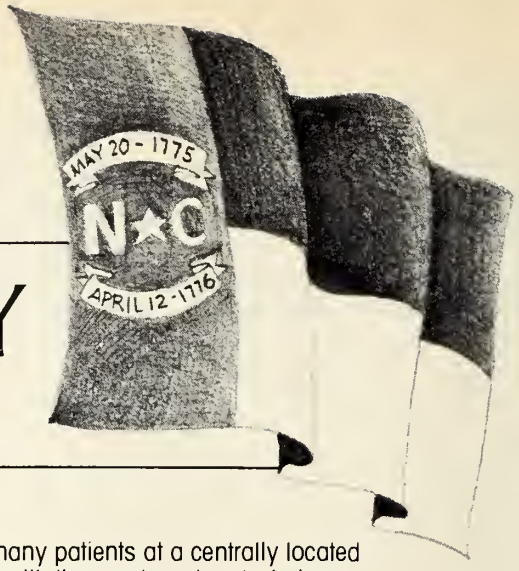
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Dr. Gaine Cannon

A modern-day version of the country doctor on horseback, Dr. Gaine Cannon covered his scattered practice around the Blue Ridge Mountain country near Balsam Grove, North Carolina, in a four-wheel-drive Jeep wagon.[1]

On an average working day, Dr. Cannon rose at sunup to see patients at his converted-farmhouse clinic before setting out to make his usual 15 to 20 house calls around the countryside. Generally, after treating his primary patient, he saw each member of the family as well—his personal effort at preventive medicine.

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With the nearest hospital some 60 miles away and no pharmacy closer than an hour-and-a-half drive, Dr. Cannon filled his own prescriptions, delivered babies and treated many patients at a centrally located general store with the most modern techniques and medications. After a day on the road—usually within a 50-mile radius—Dr. Cannon's office hours would begin at 5:30 p.m. and stretch on until the last patient was attended to. His record-keeping sessions routinely filled the hour before midnight—rounding off Dr. Cannon's 18-hour day.

At all hours

But emergencies often interrupted his sleep. Dr. Cannon claimed his real office hours were 24 hours a day, and his patients revered him for it.

Dr. Cannon died in 1966 at the age of 68. He will be long remembered—most especially by the more than 5000 North Carolinians he helped bring into the world, some of them at the side of a rutted country road.

Reference: **1.** Doctor in the backwoods, in Lee RV, Eimerl S *et al*: *The Physician*. New York, Life Science Library, Time Inc., 1967, pp. 38-50



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Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness such as operating machinery or driving a car.

References: 1. Rickels K: Drug treatment of anxiety, in *Psychopharmacology in the Practice of Medicine,* edited by Jarvik ME; New York, Appleton-Century-Crofts, 1977, p. 316. **2.** Feighner JP *et al: Psychopharmacology 61:* 217-229, Mar 1979. **3.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

In moderate depression and anxiety

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Please see summary of product information on following page.

LIMBITROL® Tablets Ⓝ Tranquilizer–Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide)

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude toxicity, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring considération because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100; Prescription Paks of 50.

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EDITORIAL

Paradoxical Times

Alfred L. Ferguson, M.D.

FEELINGS are running high, adversely it should be added, in regards to the Diagnosis Related Grouping (DRG) method for Medicare reimbursement to hospitals. One county society wrote congressmen insisting this payment mode was morally and economically wrong and should be repealed for the sake of free enterprise and as a strike against socialism. One hospital administrator copied to me a paper penned by his chief of staff for local physician dispersement addressing DRGs. The paper described October 1, 1983 as an historical date to remember as the day health care delivery became headed "down the tube."

These complaints seem legitimate enough. There appears a paradox amid all the smoke, though. While hospital administrators lament DRGs, there appeared, in the December 19, 1983 issue of *The Internist's Intercom* (Vol. 7:12), a report of . . . "recent audit of 331 hospital bills in 40 states revealed that 93% of the bills contained errors . . . 77% were errors of charges that could not be substantiated. . . . In contrast, 15% of the bills omitted charges for services rendered." Even so . . . "the errors found resulted in an average net decrease per bill of $673." The implication here is phenomenal when extrapolated to all of the hospital discharges across the nation. Assuming the *Intercom's* report is representative of most hospitals and assuming that there were ten million admissions and discharges in the USA in one year, the overbill would amount to five billion one hundred eighty-two million dollars. Regional differences and hospital sizes should be considered, however. Large urban hospitals may be more prone to overbill than small rural ones, or vice versa. Assuming that the *Intercom's* report is accurate, ponder the questions this generates. One is "Why have not the hospitals and the doctors already addressed this issue?" There have been many complaints for years about inefficient billing problems with hospitals. Most people who complain about this problem argue that there is no need to hassle with the problem since "It is so complicated I don't know where to start; and, when you do complain, the billing personnel give you such a rough time and have things so messed up it just isn't worth it. Besides, insurance will cover most of it anyway!"

Some have reported that waste and employees' pilferage in hospitals is astronomical, and no reasonable effort is exerted by the administrations to alter the situation.

Physicians pose an even greater paradox. Twenty years ago hate-government thoughts and frothing at the mouth were typical signs and symptoms endemic to physician gatherings where "socialized medicine" was the topic. Comments were heated and sounded like this: "I have always taken care of the poor, old or not, whether they could pay or not!" Another one was: "I'd as soon die or quit my practice before the government ever pays me one dime!" True enough, there have been many to quit practice and many now work for large companies or the government full time. A few went fishing early. The rest are still in there plugging away with comments now like this: "Those SOBs are still not paying me what I bill!"

The public is also a paradoxical group. Let Mr. and Mrs. John Q. Doe approach the market place and strike a bargain. It seems they have no problem settling for a smaller house or a smaller car when their budget doesn't allow the larger ones. They settle for double knit and an occasional meal out rather than high fashion and gourmet cooking. But, when it comes to medical care, they expect top of the line, comfortable, modern, expert, high-class care delivered flawlessly and fast by a wise, handsome, likable, fatherly physician assisted by a pretty, patient, capable, and loving nurse. For free! No less! "It is my right."

Then, there are the Feds; or there is the Feds. (I have never known which was correct.) They live, breathe, and generate paradox. We must give them one point, though; they never did *say* that they would cover any medical bill one hundred percent. Their sin is they imply it. They allow the press, other news media, and politicians to carry the message uninterrupted and uncorrected to the public that they will "bear the load all the way." They like to think of medical care as a truckload of goods stacked by the numbers, delivered by the pound and consumed by the ounce. Furthermore, they want the services of an all night affair in a king's harem for the price of a one-hour stand in a Hill Street "Ho House."

The federal reimbursement formulas are from outer space. No one understands them. They are disequilibrated rat-a-tat-tat, the 80% of the allowable and the allowable is less than 50% of the unrealistic. The think-tank groups who come up with these formulas designed to bewilder and frustrate do so with methodical madness. Their actions are a mockery of truth from the outset. Such behavior is unforgivable.

It seems no one thinks too clearly nowadays. No one will tell the truth. What is worse, no one knows what the truth is any more. (Of course, given time, the Feds will define it.) Why do not the hospitals admit they are wasteful and they overbill? Why do not the public and the Feds realize that "there ain't no such thing as a free lunch"? Quality medicine costs now and will cost forever. (One question comes to mind when the subject of "quality medical care" is raised. Why don't the Feds offer us *quality government*?)

Why do many doctors fail so often to value their true worth and bill accordingly? Why don't we admit we fail

From 6 Doctors Park, Greenville 27834.

frequently to be totally truthful, kind, considerate, and respectful of patients and their families? Why do we not explain things to our patients so that they can understand? Why do we not admit to them when our judgment was poor? Why are we rude sometimes just to cover up our own weaknesses and frailties? And most of all, why do we not admit that we never did take care of *all* of the poor, old or not, for free — just some of them!? Remember, neither has the lawyer defended, the preacher ministered, the grocer fed, the retailer clothed, the teacher taught, nor the realtor housed *all* of the poor, old or not, either! This just goes to show us that the sick, the illegal, the sinner, the hungry, the threadbare, the ignorant, and the homeless ye will have with you always.

Despite any thinking to the contrary, we physicians *do* owe our patients a lot, whether we like it or not. We owe them kindness, fairness, explanations, expert care, and "the time of day." Most of all, we owe them and ourselves the truth. We have no right to do otherwise. It is our heritage; if the rest of them do not follow suit that is their problem, not ours.

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The author is responsible for the accuracy of all statements and references. Acronyms and other abbreviations should be kept to a minimum; unless an acronym is widely known and used by all specialties, it should be fully explained in the text. Refer to pharmaceutical products by their generic names; brand names may follow in parentheses. Units of measure should appear in the metric system. References, typed in double-space, should be listed in the order of their citation in the text, not alphabetically. They should follow the style used in articles in the *Journal*.

Illustrations should be black and white glossy prints, with legends typed in double-space on a separate sheet of paper. The *North Carolina Medical Journal* has no budget for printing in color; any author who wishes to publish a four-color figure may negotiate to pay for the costs.

Attach to the two copies of the manuscript a covering letter giving the address and telephone number of the person who will correspond about it and address the completed communication to the Editor, Box 3910, Duke University Medical Center, Durham, NC 27710.

All manuscripts are subject to editorial changes. If extensive revision is necessary, the author will receive a draft of the edited article for approval before publication.

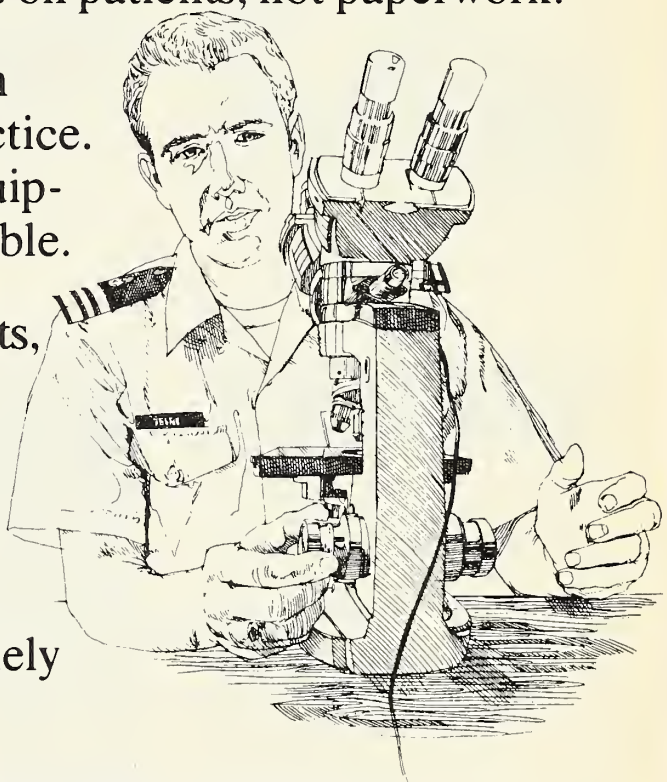
Authors interested in more effective writing may find *The Elements of Style* by Strunk and White and *How to Write and Publish a Scientific Paper* by Day helpful.

Extracted, with permission, from Virginia Medical, with thanks.

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Your Journal's Printer

Ovid H. Bell

NOW that we're into the second year of printing your *North Carolina Medical Journal,* it's high time we introduce ourselves. Perhaps some of you have wondered where Fulton, Missouri, might be, what The Ovid Bell Press, Inc., is and how it came to print your journal. At Dr. Stead's kind invitation, I will try to tell you about all three.

Fulton is a town of not quite 15,000 located 110 miles west of St. Louis and 15 miles north of the Missouri River, the county seat of Callaway County (sometimes referred to as the capital of the Kingdom of Callaway, as a result of a Civil War episode in which sovereignty was supposedly recognized by federal troops). It is the home of two state institutions, two colleges (William Woods College, for women, and Westminster College, originally for men but coeducational since 1979), and several small but nationally known industries. It is perhaps best known for the distinguished leaders who have spoken here at various times: Jefferson Davis (in 1875 to a Confederate veterans' reunion), Winston Churchill, three U. S. Presidents (Truman, Ford, Reagan) and other world figures. The town is near the center of an area often referred to as "Little Dixie" because its original settlers came from Virginia, Kentucky and the Carolinas. The Bells were not among those first settlers, but my widowed great-grandmother, Permelia Gilbert Bell, arrived by river boat in 1855 with three teen-aged sons and five slaves. The Civil War came just a few years after that tc find Missouri divided as a border state. This area was steadfast in its support of the Confederacy, and its southern attitudes, if not its accents, continue.

But how did The Ovid Bell Press, Inc., take root and grow on the Missouri prairie, near the foothills of the Ozark Mountains?

The business was begun in 1901 by my father, Ovid Bell, when he acquired a foundering weekly newspaper, which he made into a daily within a few years. A natural part of any county-seat newspaper was its job printing department, and somehow he decided to expand that into larger equipment and get into magazine and book printing. By 1926 he found two things: that the newspaper and the magazine and book printing businesses were not compatible, and that a town of 6000 could not support two daily papers. So he sold his newspaper to its rival and, on January 1, 1927, founded The Ovid Bell Press, to engage in magazine and book printing. The business was incorporated in 1936 as part of the financing program for a new building. Incidentally, I still recall his visiting me that spring (a freshman at Davidson College in your state) to learn my career plans before going ahead, and I've never regretted my commitment to the business.

From 1201-1205 Bluff Street, Fulton, MO 65251.

The business has grown steadily, and the 1936 building has been expanded, with a building addition completed in May of this year, to five times its original size. For many years we were letterpress printers, working with engraved plates and type from Linotype machines, but we have kept abreast of the trend in our industry and converted to offset printing — and we have moved consistently to maintain the highest possible "state of the art" in sheet-fed offset printing.

I can honestly say that I "grew up" in the printing business, taking the helm, at my father's death in 1953, as the company president. I was joined eleven years ago by my son John, now a vice president, and four years ago by my daughter Jane (Ackerman). It's a family business, and I cannot deny the fond hope that my two five-year-old grandsons (and perhaps my two granddaughters as well) will someday be printers here.

While I'll take some credit for the leadership given a growing business, the real key to our success over the years is the kind of people we have in our organization. Some of the "young fellows" who worked with me when I assumed the presidency thirty years ago can now boast 25-40 years' service here. Almost all are local people who have learned the printing craft in our plant, but the few "outsiders" who have joined us provide an important leavening ingredient. It's a group anybody could be proud of, for all have caught the spirit of the company, to give our customers the best we can of both craftsmanship and service.

There is a strange coincidence. The organization today consists of 81 people, from the president's office to those who clean and carry out the waste, and we are handling 82 different publications, plus the book and incidental printing we do for our regular customers. Only a few years ago 55 people were doing 35 publications; automation, faster presses, computerization — and better utilization of manpower — make the difference. Still, craftsmanship is the watchword.

Whether it's one of the Bells, vice presidents Bob Epperson or Raymond Miller, Dan Grubb (a transplanted Marylander who handles your account), one of our service representatives or foremen, clerical or production workers, each is a member of a team dedicated to serving our customers.

With a western sales office in the San Francisco area, we are serving customers from coast to coast. We print a variety of scientific and professional journals, trade magazines, fraternity and other association publications. The *North Carolina Medical Journal* is one of ten state medical journals we print, in addition to five medical specialty journals for the C. V. Mosby Company of St. Louis, *The Pharos* of Alpha Omega Alpha and *Federation Bulletin* for the Federation of State Medical Examining Boards.



This process camera provides film negatives for all materials to be printed.



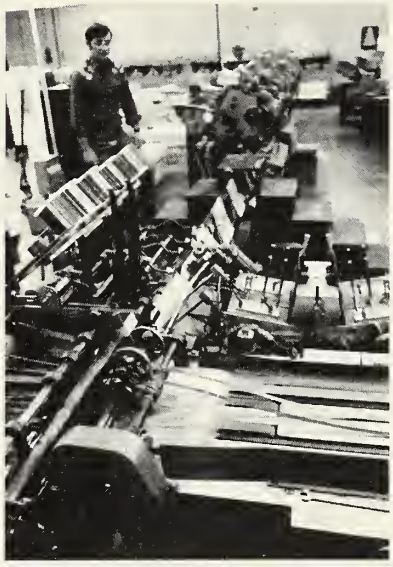
These negatives are arranged in proper combinations and stripped into "masks," large opaque sheets cut to expose only the areas to be printed.



Offset printing is a process in which an inked impression from the aluminum printing plate is made on a rubber blanketed cylinder and then transferred to the paper.



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North Carolina
MEDICAL JOURNAL
for doctors and their patients

The Patient Has a Sore Throat
By school age, children have five to six upper respiratory infections per year. Parents worry about strep throats and rheumatic fever. What should the patient and doctor do?

Strategies for Managing Terminal Cancer Pain

Physician Assistants in North Carolina: Survey Results

"Captain of All the Men of Death"

Learning Without Words

1984 Sports Symposium: June 29-July 1 Wrightsville Beach

1984 Committee Conclave, September 27-29, Southern Pines

Contents on page 279

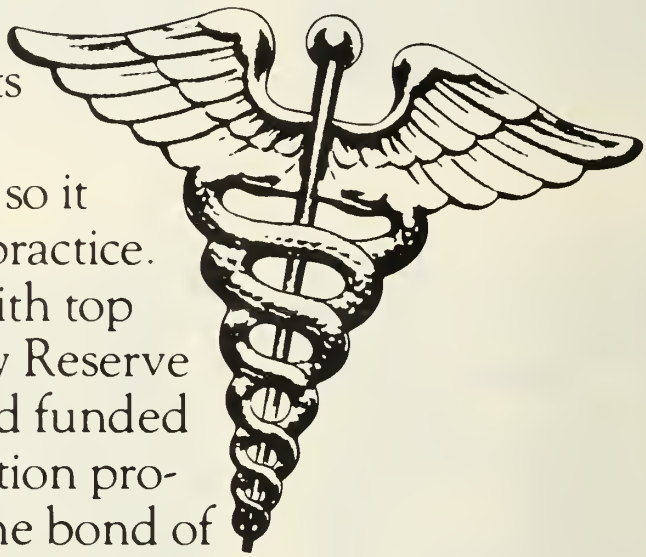
The finished product.

Our state medical journal business began logically enough with *Missouri Medicine*, and the Missouri State Medical Association is one of three customers whom we have served more than 50 years. The Iowa and Kansas journals came in the early 1950s, followed by Mississippi, Georgia, Alabama, Louisiana, Rhode Island, North Carolina, and South Dakota. Our experience with medical texts and illustrations has been enhanced by book work for Charles C Thomas, Publisher and Year Book Medical Publishers. Our interest in overall publishing, advertising and mailing requirements, along with our long-time working relationship with the State Medical Journal Advertising Bureau (of which your journal is a charter member), has made it possible for us to offer an attractive package to each of the state medical societies we serve.

In its 57th year, The Ovid Bell Press looks to the future with plans for continuing growth and keeping pace with the rapidly changing technology of our industry — all to serve our customers better. We hope that North Carolina doctors will for many years to come be reading a journal we have printed for them in Fulton, Missouri.

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Two Especially Noteworthy CMEs

FALL TOUR OF SPAIN

The North Carolina Medical Society invites its members, their spouses, and their guests to join a Fall tour of Spain.

The nine-day (October 13-21) tour of Madrid and the Andalusia region is specially designed to blend the professional and tax advantages of continuing medical education with the excitement and fun of vacation travel.

The CME program, which combines lectures by the faculty of the Autonomous University of Madrid with visits to Spanish hospitals and clinics, has been reviewed and is acceptable for 20 hours prescribed credit by the American Academy of Family Physicians.

The Society-endorsed trip was planned in association with Mr. Jose Infante, President of J. M. Sales, Inc., and the American Leadership Study Groups, an educational travel organization based in Worcester, Massachusetts. Born in Cuba, Mr. Infante is an American citizen and a longtime Raleigh resident who has worked for the N.C. Department of Public Instruction. He will lead the tour.

The trip includes: a round-trip flight via scheduled airline



from Raleigh-Durham (RDU) or Charlotte airport to Madrid; seven nights' accommodations and breakfasts in a deluxe, five-star hotel in central Madrid; a gala dinner with Spanish physicians and their spouses; airport transfer, baggage handling, and travel insurance; a fashion show and a demonstration of Spanish culinary art; half-day sightseeing in Madrid and its environs with professional guides; a hospitality desk with local tour information and suggestions; and welcome and farewell cocktail parties.

Trip costs are $1,495 per person from RDU or $1,569 per person from Charlotte. The $300 seminar fee and the fees for optional excursions are extra.

All Society members should have already received a brochure and a registration form for the trip.

Society members, spouses, and their friends are urged to complete the accompanying registration form and join this custom-tailored tour of Spain.

Physician Seminar in Madrid, Spain

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(To be completed by applicant)

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Address _____ Date of birth: _____
City _____ State ____ Zip _____ Sex: _____
Office phone (___) _____
Home phone (___) _____
Passport No. _____ Expiration date: _____

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Name _____ Date of birth _____
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_____ VISA No. _____ Amount to be charged _____
_____ Check _____

Signature _____ Today's Date: _____

ETHICS CONFERENCE AT GRAYLYN

You are cordially invited to attend "Medical Ethics In An Age of Science" on August 10-11 at the Graylyn Conference Center in Winston-Salem. The North Carolina Medical Society and Bowman Gray School of Medicine of Wake Forest University are co-sponsoring this conference, which will brief state leaders in medicine, business, religion, and education on the ethical challenges presented by new medical technology, reduced funding for medical care, and changing values.

The conference is a project of the Society's Committee on Ethics & Religion, formerly chaired by Gloria F. Graham, M.D., of Wilson. Richard Janeway, M.D., Dean of Bowman Gray School of Medicine, will serve as the conference moderator.

The roster of distinguished speakers includes:

Dr. Thomas K. Hearn, President, Wake Forest University; Edmund D. Pellegrino, M.D., John Carroll Professor of Medicine & Medical Humanities, Georgetown University Medical Center; Dr. J. Stanley McQuade, Lynch Professor of Law, Campbell University; Mr. Kevin Murphy, Vice President, First Union National Bank; Mr. Calvin Michaels, Director of Personnel, Burlington Industries; Mr. Don Patterson, Program Administrator, IBM, Research Triangle Park; and Stuart Bondurant, M.D., Dean, UNC School of Medicine, Chapel Hill.

Graylyn Conference Center was the home of industrialist Bowman Gray, and is the second-largest private home ever built in North Carolina. It is a national historic landmark, now operated as a conference center by Wake Forest University. Graylyn is a splendid and unique facility located on a 55-acre estate.

Conference check-in begins at 5 p.m. on Friday, August 10, followed by a cocktail reception, dinner, and the dinner speaker. The conference concludes after lunch on Saturday, August 11. A complete hourly schedule will be mailed to registrants.

Accommodation and conference fees include the cost of three meals and the reception for attendees. Conference spaces are limited. You are urged to complete and mail the registration slip below as soon as possible. Make checks payable to the North Carolina Medical Society.



Please register me for:
Medical Ethics In An Age of Science — August 10-11, 1984
Graylyn Conference Center
Winston-Salem, N.C.

_____ name(s)

_____ title — organization

_____ address

_____ city/state/zip

_____ telephone number

room rate $125 (single) or $175 (double) _____

conference fee $75 (per person) _____

OR

conference fee $100 (day visitors only) (per person) _____

total enclosed _____

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George Richardson
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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

July 18

Hospital Nutrition Update
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St., Sanford 27330, 919/774-4100, ext 394

July 19-21

Sixth Annual Mountain Meeting
Place: Asheville
Credit: 12 hours, Category I AMA
Fee: $150
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

July 30-August 3

Diagnostic Imaging
Place: Atlantic Beach
Fee: $425
Credit: 25 hours
Info: J. D. Wright, Box 3808, Duke Hospital, Durham 27710. 919/681-2711

August 4

Geriatric Education Day
Place: Raleigh
Credit: 4 hours
Info: NCAFP 919/781-6457

August 7

Malpractice Awareness — STAT
Place: Greensboro
Info: Wayne Parker. 919/828-9334

August 14

Malpractice Awareness — STAT
Place: Charlotte
Info: Wayne Parker. 919/828-9334

August 15

Electrolytes/Arterial Blood Gases/Fluid Balance
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St, Sanford 27330. 919/774-4100, ext 394

August 21

Malpractice Awareness — STAT
Place: Goldsboro
Info: Wayne Parker. 919/828-9334

August 24, 26

Summer Urology Conference
Place: Winston-Salem
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

September 9-12

Basic Clinical Teaching Skills
Place: Rougemont
Credit: 20 hours Category I and AAFP
Info: Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571.

September 9-13

Clinical Skills Workshops and Review
Place: Winston-Salem
Credit: 31 hours Category I
Fee: $395
Info: Elizabeth B. Philp, Department of Family Medicine, Bowman Gray School of Medicine, Winston-Salem 27103.

September 11

New Developments in Clinical Medicine
Place: Fayetteville
Credit: 7 hours AAFP
Info: Mary Henley. 919/323-1152.

September 21

Sixth Annual Health Law Forum
Place: Greenville
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200.

September 21-22

New Advances in the Treatment of Sickle Cell Disease
Place: Wrightsville Beach
Credit: 8 hours Category I
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878.

September 28-29

Adolescent Health Issues: Challenges for the 1980s
Place: Durham
Credit: 9 hours Category I
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878.

OUT OF STATE

July 26-28

6th Annual Pediatrics Primary Care Conference
Place: Virginia Beach, VA
Credit: 12 hours
Fee: $275
Info: S. Rosner, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

July 30-August 3

12th Annual Beach Workshop
Place: Myrtle Beach, SC
Credit: 20 hours AMA Category I
Fee: $225
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

August 12-17

Symposium on the Surgical Treatment of Cancer
Place: Orlando, FL
Credit: 20 hours Category I AMA
Info: C. Easterling, Box 3108 Duke Hospital, Durham 27710. 919/684-6878

September 6-8

Doppler Echocardiography
Place: Charleston, SC
Credit: 24 hours Category 1
Fee: $350
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103. 919/748-4450.

September 13-15

Advanced Applied Ultrasound in Obstetrics
Place: Myrtle Beach, SC
Credit: 12 hours Category I
Fee: $350
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103. 919/748-4505.

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Surgeon, Durham, NC, and
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Letters to the Editor

Cephalosporin Allergy

To the Editor:

This letter is in reference to your article, The Patient Has a Sore Throat. What Should the Patient and Doctor Do? (NCMJ 1984;45:309-312, May). In the article it was said, "For the patient who is allergic to penicillin, oral erythromycin is the antibiotic of choice. For the rare patient who cannot tolerate either of these two drugs, an oral cephalosporin or clindamycin can be used."

It is important to note, and many physicians may not know, that 25 to 50 percent of the patients allergic to penicillin may be sensitive to cephalosporin.

Claude A. Frazier, M.D.
Doctors Park
Asheville 28801

Strategies for Pain Management in Terminal Cancer

To the Editor:

Congratulations to you and your staff on publishing an excellent article (NCMJ 1984;45:283-290, May). Dr. Linda Frazier and Errol Kohl have written one of the most accurate an significant articles on the subject of pain and the terminal patient. Their assessment of an actual problem with its solution indicates deep humanity and compassion for the subject.

The case representation is a perfect example of the bind the patient is caught in when priorities are not uniformly set to meet needs. I truly hope that physicians not only read this article, but absorb the sound advice. More importantly, let us hope they use the recommended strategies in their medical practices.

Thank you for the support this article has given me and for the help it will bring to the terminal patient.

Eileen Bardsley, R.T.
1310 Crestview Drive
Shelby 28150

Words of Praise for Words of Wisdom

To the Editor:

John Graham's editorial (NCMJ 1984;45:325-326, May) is a jewel obviously formed by the crystallization of vast experience over substantial time in an atmosphere of institutional heat and pressure. I offer two observations.

Not once did Dr. Graham use the word "power."

Dr. Graham's admonitions, I fear, can be learned but not taught.

David L. Silber, M.D.
Moses H.Cone Memorial Hospital
Greensboro 27401

In Opposition to Moonlighting

To the Editor:

The discussion of moonlighting by family medicine residents (NCMJ 1984;45:247-248, April) approaches the subject only from the perspective of its impact on medical education. Patient care may be by far the more important issue.

Residents moonlight not to increase outpatient encounters, but instead to earn extra income. They perform as "attending physicians" and accept wages determined by the laws of supply and demand. Moonlighting usually occurs in hospital emergency departments and private primary care clinics. Patients presenting to hospital emergency departments deserve care from physicians competent to practice the specialty of emergency medicine. Residents could hardly moonlight as radiologists, gynecologists, neurologists, or orthopaedists . . . why, then, should we condone the practice of emergency medicine by physicians still in training?

Emergency medicine specialists possess skills most family medicine residents do not have. True emergencies often cannot wait for an on-call specialist to come from home to the hospital.

If family medicine residents require additional outpatient encounters, as Kelly and Sharp suggest, these should be well-supervised and preferably under the auspices of their training program.

Dean Dobkin, M.D.
6817 El Greco Court
Pineville 28134

Fentanyl

To the Editor:

This office wishes to call the attention of your readers to information we have received regarding the diversion and abuse of fentanyl related chemicals among some elements of the medical community. Our concerns are particularly directed to personnel assigned to operating rooms where the drug is used as an anesthetic. Reliable sources lead us to believe that fentanyl and/or certain of its analogs have been the cause of diversion, abuse, and death in this state, as well as in other locations throughout the country.

Fentanyl is a synthetic anesthetic currently used in hospitals under the brand names of Innovar or Sublimaze and will produce the classic narcotic effects including euphoria, suppression of body functions and death. An almost limitless number of analogs or variations of fentanyl can be produced with potencies ranging from 80 times that of morphine and up.

This drug also is sold on the streets under the name "China White." Even though its presence among street addicts in North Carolina is nominal at present, we are expecting a substantial increase in overdose emergencies at any time. Our information from the Department of Alcohol and Drug Programs in California is that thirty plus deaths have occurred in that state where the cause of death can be directly identified as one of the fentanyl analogs. Some of the identified street analogs are 3-methyl fentanyl, alpha methyl fentanyl, and para floral fentanyl. Since there is a suspicion that a very substantial portion of all heroin sold in

California may actually be an illicitly manufactured form of fentanyl, there is an added concern for its eventual impact on our state. Fentanyl-like chemicals are *not detectable* by the usual laboratory drug screens. Therefore, it is believed that narcotic overdose deaths may be caused by fentanyl analogs.

Due to the extreme danger related to the misuse and abuse of this drug, I would appreciate being notified when diversion is suspected or when technical assistance is needed in making identification.

Steven L. Hicks, Deputy Director
Alcohol and Drug Abuse Services
325 N. Salisbury Street
Raleigh 27611

We Thought You'd Like to Know

Resolution from Buncombe County at NCMS Annual Meeting, May 1984

WHEREAS, several years ago *The North Carolina Medical Journal* came under extreme criticism for failing to be an effective vehicle for the North Carolina Medical Society; and

WHEREAS, the Buncombe County Medical Society, among others, led the battle to effect improvement or dissolution of *The Journal;* and

WHEREAS, the House of Delegates in 1982 mandated a vigorous attempt to upgrade *The Journal;* and

WHEREAS, since January 1, 1983, under the Editorship of Eugene A. Stead, Jr., M.D., along with a new staff of assistants, *The Journal* has markedly improved in quality, format, interest, and general usefulness; and

WHEREAS, the "Features for Patients" section has been praised warmly by our patients; therefore be it

RESOLVED, that this House of Delegates of 1984 go on record as warmly congratulating the current editor, his staff and the many physicians of the State Society who have worked to improve *The Journal.*

Report of the Ad Hoc Committee to Evaluate the *North Carolina Medical Journal*

We have continued to review the *North Carolina Medical Journal* from 1982 to the present. We have followed the costs of the *Journal* for 1982 and 1983, and have seen the proposed budget for 1984. We have also studied the results of the Tarrance & Associates phone survey and read the Annual Report of the *Journal's* Editorial Board.

The features of the *Journal* that were introduced in 1982 have been maintained. A recent issue contained 15 articles and the "Features for Patients" section. The topics were varied and timely.

The cost of the *Journal* in 1982 was $15.19 per member. The 1983 cost was $14.00 per member. The projected cost for 1984 will be slightly less if membership increases.

The phone survey revealed that 71% of the membership sample read the *Journal* totally or in part; 56% of our membership felt that the *Journal* should be enlarged; 17% of the sample felt that the *Journal* should be discontinued if, for financial reasons, the North Carolina Medical Society needed to consider the future of the *Journal.*

The *North Carolina Medical Journal* was not placed under the Department of Communications as we recommended. We do not feel that the failure to do this has been detrimental either to the *Journal* under the editorship of Dr. E. A. Stead, Jr., or to the efforts of Mr. Tom Bennett, the Communications Director.

Mr. Speaker, members of the House of Delegates, the ad hoc Committee to Evaluate the *North Carolina Medical Journal* reports that the Editorial Board and the Staff have continued the improvements started in 1982 and 1983. We compliment them for doing so without increasing costs. *We recommend that the North Carolina Medical Journal continue to serve our membership in the future as in the past.*

I appreciate the efforts of Dr. Susan Gustke and Dr. Phil Naumoff in the compilation of this report.

William W. Fore, M.D., Chairman
1705 W. Sixth Street
Greenville 27834

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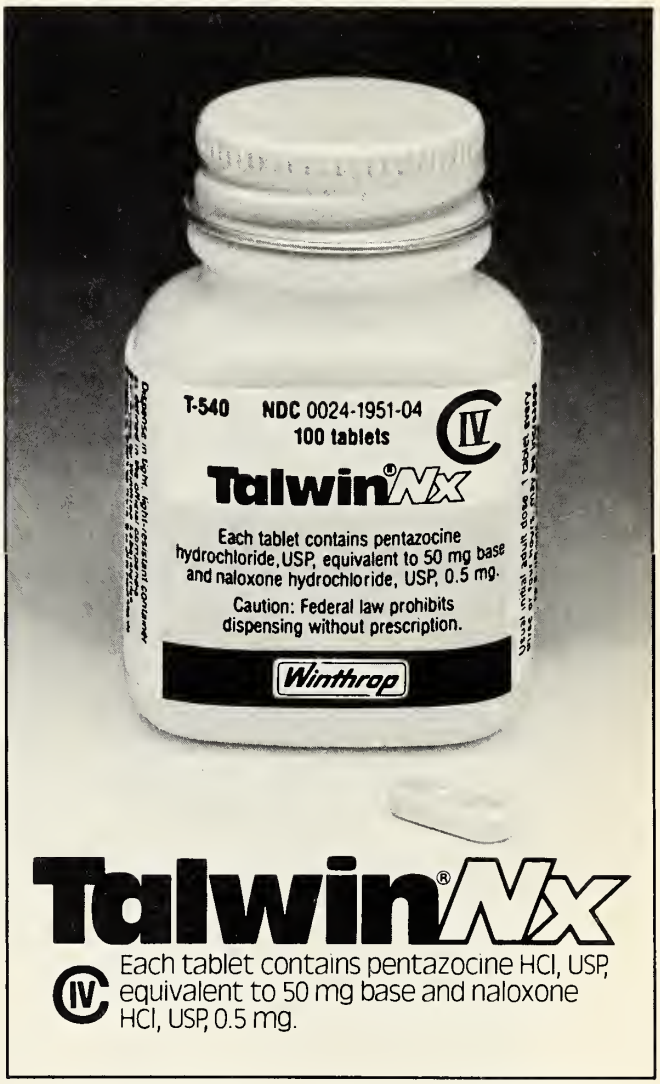
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The original formulation had been subject to a form of misuse among street abusers known as "T's and Blues." TALWIN 50 and PBZ,* an antihistamine, would be ground up together, put into solution, and injected intravenously. The combination produced a heroin-like high. Because naloxone is a narcotic antagonist when injected intravenously, it acts to nullify any high a "T's and Blues" addict might expect from the pentazocine in a combination of TALWIN Nx and PBZ. When taken as directed orally, the naloxone component of TALWIN Nx is inactive. Thus, TALWIN Nx continues to be a safe, effective, oral analgesic for the relief of moderate to severe pain, now providing added security against misuse.

*Registered trademark of Ciba-Geigy Corp for tripelennamine.



The reformulation of Talwin 50 to Talwin Nx involved the addition of 0.5 mg naloxone to help prevent misuse by injection.

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Please see following page for Brief Summary.

Talwin® Nx IV©

Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, 0 5 mg

Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone

TALWIN® Nx is intended for oral use only Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances (See **Drug Abuse and Dependence** section.)

Warnings: *Drug Dependence* Can cause physical and psychological dependence (See **Drug Abuse and Dependence**.) *Head Injury and Increased Intracranial Pressure* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention; these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure Can obscure the clinical course of patients with head injuries; in such patients, use with extreme caution and only if deemed essential *Usage with Alcohol* Due to potential for increased CNS depressant effects, alcohol should be used with caution *Patients Receiving Narcotics* Pentazocine is a mild narcotic antagonist Withdrawal symptoms have occurred in patients previously given narcotics, including methadone *Certain Respiratory Conditions* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis

Precautions: *CNS Effect* Use cautiously in patients prone to seizures, seizures have occurred though no cause and effect relationship has been established. Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours Such patients should be very closely observed and vital signs checked, if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur *Impaired Renal or Hepatic Function* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects; it should be administered with caution in renal or hepatic impairment In long-term use, precautions should be taken to avoid increases in dose by the patient *Biliary Surgery* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures, the clinical significance of these findings is not yet known *Information for Patients* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants *Myocardial Infarction* Use with caution in patients with myocardial infarction who have nausea or vomiting *Drug Interactions Usage with Alcohol* See **Warnings.** *Carcinogenesis, Mutagenesis, Impairment of Fertility* No long-term studies in animals to test for carcinogenesis have been performed. *Pregnancy Category C* Should be given to pregnant women only if clearly needed *Labor and Delivery* Use with caution in women delivering premature infants Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown *Nursing Mothers* Caution should be exercised when administered to a nursing woman *Pediatric Use* Safety and effectiveness in children below the age of 12 years have not been established

Adverse Reactions: *Cardiovascular* Hypotension, tachycardia, syncope *Respiratory* Rarely, respiratory depression *CNS Acute CNS Manifestations* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted *Other CNS Effects* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor *Gastrointestinal* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress *Allergic* Edema of the face, dermatitis, including pruritus, flushed skin, including plethora *Ophthalmic* Visual blurring and focusing difficulty *Hematologic* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia *Other* Headache, chills, insomnia, weakness, urinary retention.

Drug Abuse and Dependence: *Controlled Substance* TALWIN Nx is a Schedule IV controlled substance

Dependence and withdrawal symptoms have been reported with orally administered pentazocine Patients with a history of drug dependence should be under close supervision. Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient Tolerance to the analgesic effect is rarely reported, there is no long-term experience with oral use of TALWIN Nx

The amount of naloxone present (0 5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine, however, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals

Overdosage: *Treatment* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated Assisted or controlled ventilation should also be considered For respiratory depression, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist

Please consult full product information before prescribing

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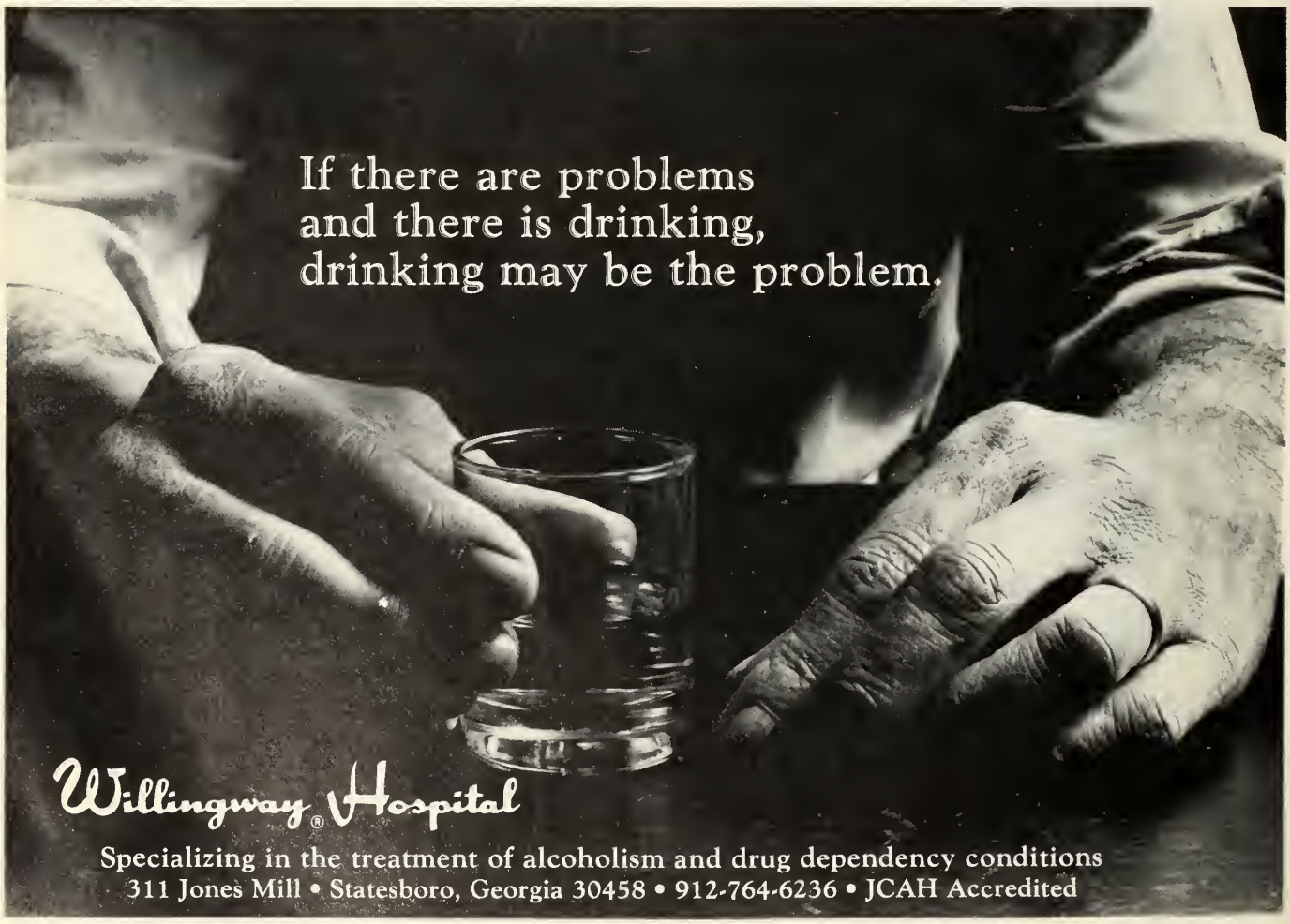
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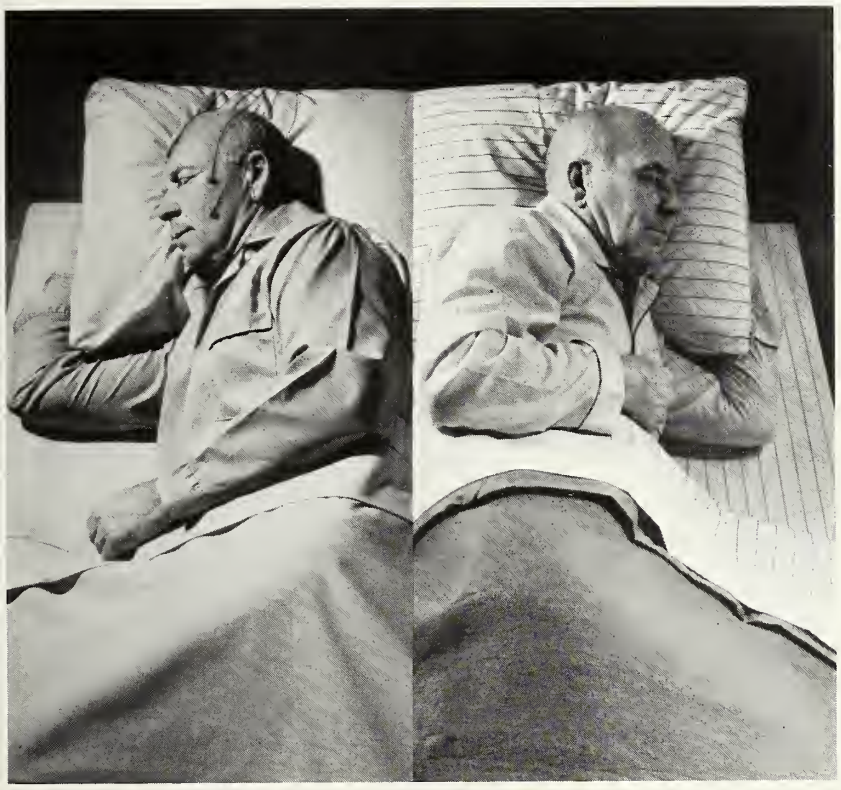
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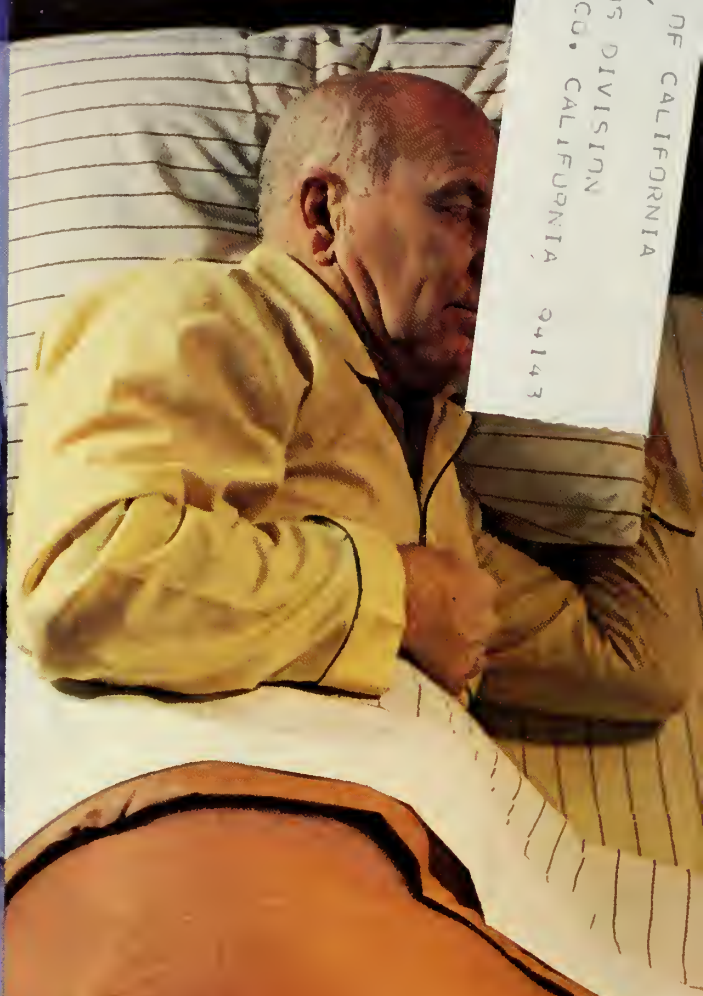
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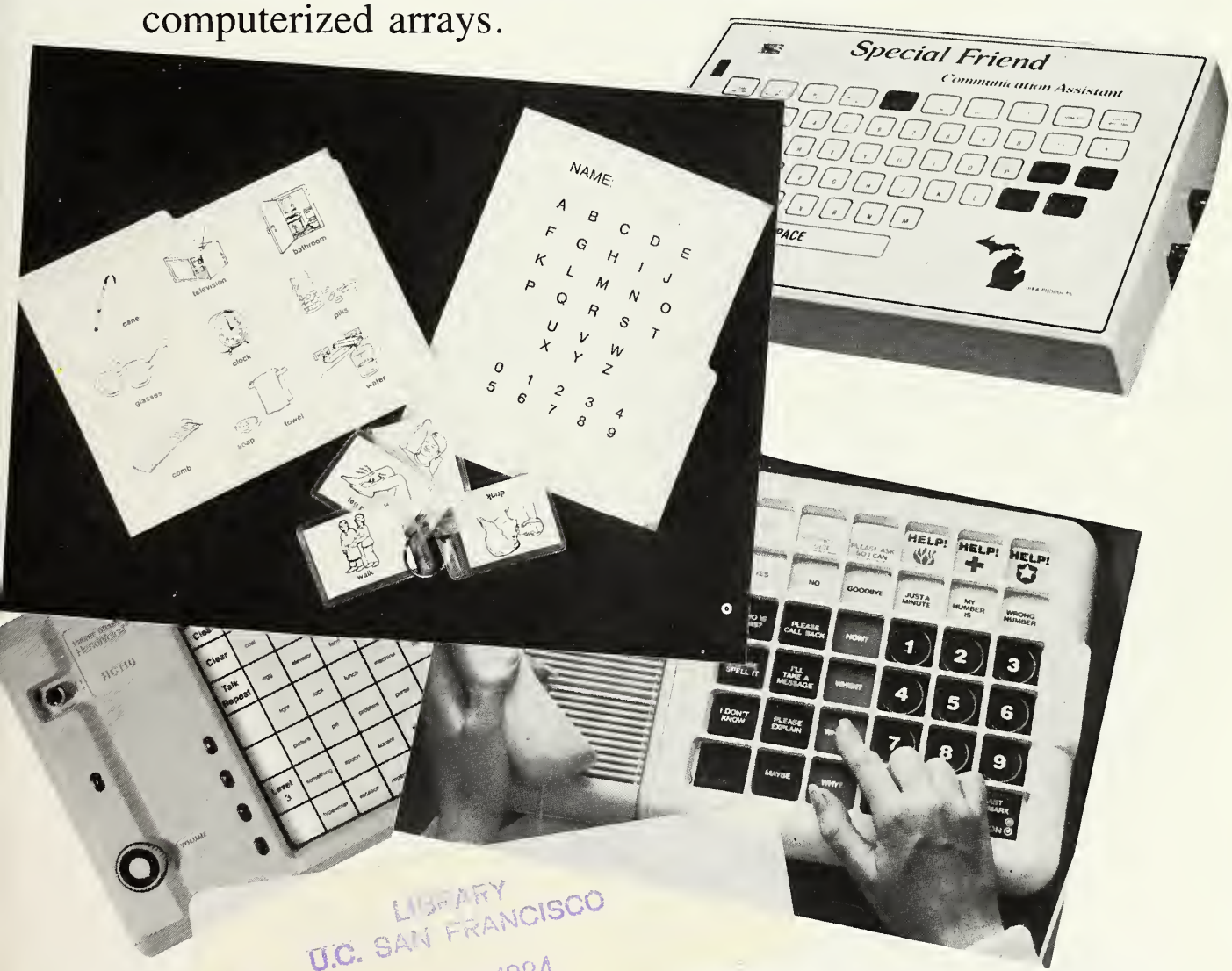
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by Jennifer Horner, Ph.D., page 503

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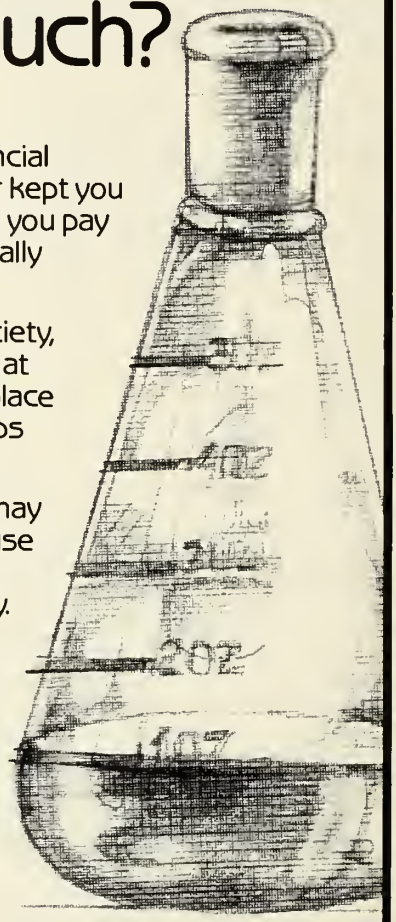
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Sports Medicine Kit

James D. Hundley, M.D.

MY first experience as a sideline physician was at a high school football game. A fellow orthopaedic surgeon was a team physician and accepted the responsibility for covering all home and most out-of-town games for a local school. For the home game that Friday he had to be away.

Having completed a residency in orthopaedic surgery and two years in the armed services, I felt comfortable in the anticipation of management of whatever injuries may occur. I took the little black bag he handed me and went to the game.

My first glance into the bag was fortunately the biggest surprise of the evening. It contained a stethoscope, a percussion hammer, a tuning fork, some tongue blades, a sphygmomanometer, and a combination otoscope-ophthalmoscope. I had nothing with which to TREAT anything. Not only would I have been at the mercy of the student trainer for injury equipment but, had a spectator had an emergency medical problem, I would have been unable to do much more than ride with him in an ambulance to an emergency room. Needless to say, during that evening I worried about more important outcomes than the game score.

Soon after that game an article by Ben R. Mayne, M.D., was published in *The Physician and Sports Medicine*.[1] In that article Dr. Mayne discussed the need for a well-equipped sports medicine bag, provided a list of essential equipment, and suggested using a large fishing-tackle box instead of a black bag (figure 1). That list was slightly revised after consultation with other orthopaedic surgeons, cardiologists, and anesthesiologists. It was then submitted to the members of the North Carolina Medical Society's Committee on the Medical Aspects of Sports and revised again. The list has been revised annually since 1976 using our own experience and that of colleagues in otolaryngology, neurosurgery, and general surgery, as well as those mentioned earlier. It has also been compared with the list in an article by James M. Glick, M.D. published in *Orthopaedic Clinics of North America*.[2]

Consideration of the following points should precede the listing of the contents of the kit:

1. No kit of manageable size and shape can contain everything one may need in an emergency situation. Each physician must decide for himself what the essential items are.

From the Wilmington Orthopedic Group, 2001 S. 17th Street, Wilmington 28401-6693.

The author is grateful to the New Hanover-Pender Medical Society and the Committee on the Medical Aspects of Sports of the North Carolina Medical Society for their help in developing and refining the sports medicine kit.



Figure 1.



Figure 2.

The Physician's Sports Medicine Kit

I. Diagnostic Equipment
- 1 Stethoscope
- 1 Otoscope/Ophthalmoscope
- 10 Tongue Blades
- 1 Percussion Hammer
- 1 Sphygmomanometer

II. Emergency Airway Equipment
- 1 Padded Tongue Blade
- 1 Bite Screw
- 2 Oral Airways (1 medium and 1 large)
- 2 Nasal Airways (sizes 26 and 34)
- 3 Endotracheal Tubes with Inflatable Cuff (sizes 6, 7, and 8mm. I.D.)
- Stylet for Endotracheal Tubes
- 2 10cc. Syringes to inflate cuffs
- 1 Laryngoscope with 2 Blades (1 straight and 1 curved)
- 1 Ambu Bag with 2 masks (1 large and 1 small) and Attachments for Endotracheal Tube
- 1 50cc. Syringe and Tubing for Suction
- 1 Towel Clip

III. Medicines and Parenteral Access Equipment
- 2 Ammonia Inhalants
- 2 Vials Epinephrine 1:1000
- 1 10cc. Abboject Syringe with 1:10,000 Epinephrine and Cardiac Needle
- 1 5ml. Abboject Syringe with 2% Lidocaine Hydrochloride for Cardiac Arrythmias
- 1 10ml. Vial of Tensilon
- 1 10mg. Vial Injectable Valium
- 2 20mg. Vials Benadryl
- 2 50mg. Vials Demerol
- 2 50cc. Ampules of Sodium Bicarbonate
- 1 50cc. Ampule of $D_{50}W$
- 1 50mg. Vial Decadron
- 1 50mg. Vial Atropine
- 1 Isuprel Mistometer
- 2 5cc. Syringes
- 3 3cc. Syringes
- 2 18g. Needles
- 3 22g. Needles
- 3 25g. Needles
- 2 #14 Intracaths for Subclavian Venipuncture
- 4 Alcohol Swabs

IV. Eye Materials
- 4 Fluor-I-Strips
- 1 Irrigation Container of Ophthalmic Irrigation Solution

V. Suturing and Wound Equipment
- 1 Suture Set to contain:
  - 1 Needle Holder
  - 2 Hemostats — small
  - 1 Hemostat — large
  - 1 Forceps
  - 1 Suture Scissor
  - 1 Scalpel Handle and 2 Blades
  - 1 Allis Clamp
- 3 Packs of Suture
- 2 1oz. Packs of Betadine Solution
- 1 50ml. Vial of 1% Xylocaine
- 1 Tube Neosporin-G Cream
- 2 Pairs Sterile Gloves
- 1 Disposable Sterile Field
- 1 Disposable Fenestrated Drape

VI. Bandages and Splints
- 20 Band-Aids — standard
- 5 Band-Aids — large
- 5 4x4 Gauze Sponges
- 5 2x2 Gauze Sponges
- 2 2in. Rolls Kling Gauze
- 1 4in. Elastic Bandage
- 2 3in. Elastic Bandages
- 3 Rolls 4in. Plaster
- 3 Rolls 3in. Cast Padding
- 2 Foam Covered Aluminum Finger Splints
- 2 Triangular Slings
- 2 1in. Rolls Adhesive Tape
- 1 Bandage Scissor

Equipment Schools Should Have (not included in the sports medicine kit)
- 1 Bolt Cutter — double action
- 1 Stretcher
- 1 Backboard
- 2 Blankets
- 4 Sandbags
- 2 Pair Crutches — adjustable lengths
- 3 Slings
- 4 Splints — 2 upper extremity and 2 lower extremity
- 36 Rubberized Elastic Bandages:
  - 12 3 inch
  - 12 4 inch
  - 12 6 inch
- Ice — with small plastic bags for containers

2. Athletes are not the only potential patients at athletic events. Should any onlooker suffer any significant medical problem, the team physician is the most visible and possibly the only equipped doctor available. He should expect to be the first called.

3. No individual physician should be expected to treat every conceivable emergency nor should he necessarily know all possible applications of everything in his kit. At many games, other physicians will be in attendance and they may be able to help out. But, they can do little without the appropriate equipment. Those needs should be considered.

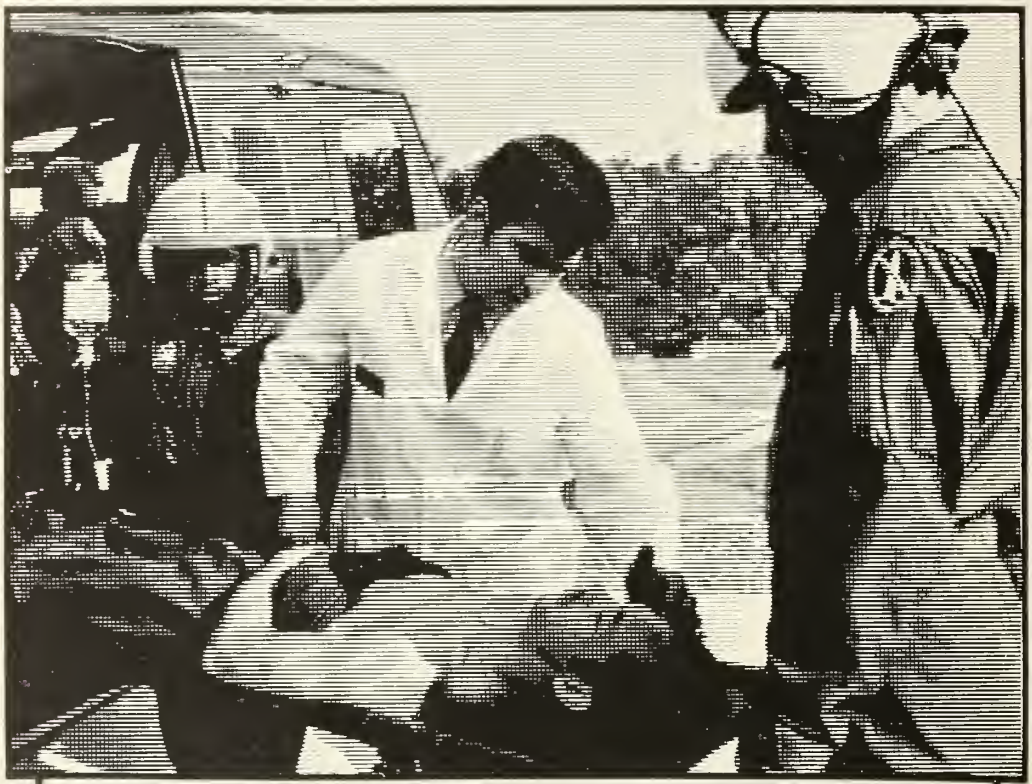
4. A plastic tackle box makes an excellent kit. It is tough, waterproof, relatively inexpensive, and doesn't look like a doctor's bag. Those qualities help make it durable, easy to replace, and less likely to be stolen. Best of all, it offers numerous small compartments which allow a flexible organization of its contents in any fashion desired (figure 2). This flexibility is at least one quality that makes it superior to commercially available emergency kits which generally have compartments preformed to accommodate specific drugs and equipment. Last but not least, one can sit on it if the bench is full and stand on it to better see the game.

5. The stocked kit is expensive. The total cost in 1984 would be five hundred and seventy-five ($575) dollars. It is worth every penny!

References

1. Mayne BR: If sports medicine is your bag — equip it well. Phys Sports Med 1975;3:67-71.
2. Glick JM: The doctor's bag. Ortho Clin North Am 1983;14:323-336.

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After Fluoride Come Sealants: A New Epoch in Control of Dental Caries

James W. Bawden

THE benefits of dental research are having profound positive effects on the occurrence and pattern of dental decay in the American population, especially in chldren and young adults. These advances offer a bright promise of improved dental health for future generations.

There are extensive studies documenting the steady and significant decline in dental caries in most segments of the U.S. population. Depending upon the population group and the index used to measure the caries rate in the given study, caries reductions of up to 50% over the last 15 years have been documented. Those of us who have been seeing children in the dental office over the past decade and a half need no statistics to understand that many more children are caries free or have very few cavities than was the case in the late '60s. The child who suffers from rampant decay and severe destruction of the teeth is much less common these days. This change is of great benefit to the general health and well being of these young people and represents enormous savings in the cost of dental care for children and young adults. We predict that as these young people grow into middle age and later life these benefits will continue.

The biggest reductions in dental decay are associated with the fluoridation of municipal water supplies, but substantial reductions are seen in nonfluoridated communities as well, presumably because of the widespread use of fluoridated toothpastes and fluoride mouth rinses and the application of topical fluorides to children's teeth in dental offices. Other factors may be involved such as changes in dietary habits, improved oral hygiene, and increased exposure of children to antibiotics for medical reasons. However, the impact of these influences is not well defined and most of the credit must be given to the effective use of fluorides.

In addition to reducing the overall occurrence of dental decay in the population, fluorides have changed the pattern of caries distribution in the mouth. Fluorides are effective in preventing decay on all surfaces of the teeth, but are most effective on the smooth surfaces between the teeth and facing the tongue and cheeks. The chewing surfaces of the back teeth which contain deep pits and grooves receive less protection from fluorides. Consequently, dental decay in the young population is becoming primarily a pit and fissure surface disease. In children exposed to fluorides, particularly fluorides in the water supply, virtually all of the decay is found in the pit and fissure surfaces.

Fortunately, another breakthrough in research has given us a new weapon in the prevention of pit and fissure caries — the dental sealant. Sealants are plastic coatings that are bonded to the pit and fissure surfaces of the posterior teeth. Application of these sealants is relatively easy and painless. The procedure is noninvasive. That is to say, a dentist need not give an anesthetic injection and no tooth structure is removed in the process. When properly placed, sealants are highly effective in the prevention of pit and fissure caries.

To place a sealant, the tooth surface to be sealed is cleaned and isolated, usually with cotton rolls, so that it can be kept free from saliva contamination for several minutes. The enamel surface is etched with an acid solution that creates millions of micropores in the enamel surface. After approximately 1 minute, the etchant is rinsed from the tooth and the tooth is dried. The unpolymerized plastic sealant is applied over the tooth surface where etching has occurred and hardens either by autopolymerization or by activation with ultraviolet or strong white light. The curing process takes from 20-30 seconds. The procedure for a single tooth can be accomplished in a few minutes. The major difficulty is that certain teeth are difficult to isolate satisfactorily and contamination of the enamel surface occurs before the procedure can be completed. If contamination occurs, the sealant will fail to bond properly and will be lost immediately or during the next several weeks. If a good bond is achieved, the sealant will stay in place for many years and fully protect the surface from dental decay.

Sealants have been available for over 15 years, but their use has been limited. The first sealant systems were not adequately tested and the failure rate was very high. Dentists became discouraged with this initial experience and they have been cautious in using the method again. There are now numerous clinical trials that clearly document the effectiveness of sealant products now on the market. There was also concern that small cavities might be covered over with sealants and there was no research on the consequences. Several recent studies have shown that sealing over small areas of decay will simply arrest the decay process since the sealing action deprives the cariogenic bacteria of their critical nutrient, sugar. The bacterial population in such cavities declines rapidly and often disappears completely. The few bacteria that may remain cannot produce acid which is necessary for the decay to progress. It is now apparent that sealants are highly effective and that the original concern about sealing over small cavities is no longer a consideration.

In December 1983, the National Institute of Dental Research sponsored a conference at which there was a complete review of all the research relevant to the use of dental sealants. An expert panel developed a consensus report which was then presented to, and commented on by, the

From the Dental Research Center, The University of North Carolina, Chapel Hill 27514.

audience of more than 500 interested scientists and clinicians. These comments were considered and a final draft of the report was produced and published by the Institute. The report has received considerable attention from the news media and has substantially heightened the awareness of the general public concerning sealants. It has also provided the dental profession with a comprehensive review and evaluation of pertinent research, and calls to their attention the scientifically documented safety and effectiveness of the method. The use of sealants by dental practitioners will probably increase substantially in the next few years and will have a most favorable effect on further reducing the caries level in our population.

Parents should rely on the clinical judgment of their dentist to decide if children should have sealants applied to their teeth. There are some children who are so resistant to decay that the use of sealants is a waste of time and money. There are others who are relatively susceptible to caries and will benefit greatly from the application of sealants to all of their pit and fissure surfaces. And in some children only selected teeth should be sealed.

These advances in the prevention of dental disease are exciting and will work to the health and well being of most of our population. They are another example of the benefits derived from the expenditure of federal tax revenues in support of biomedical research sponsored by the National Institutes of Health in the quest to more effectively prevent and treat disease. The cost of such research is considerable, but it is miniscule in the context of the improved health to be enjoyed by our population and the enormous reductions in the cost of maintaining good oral health.

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Professional Review Organizations

H. E. Strawcutter, M.D.

THE issue now, as it has been since Medicare and other third party reimbursement began, is not "whether" there will be review but "how" and "by whom."

With the advent of Medicare and Medicaid in 1965, the federal government immediately became the largest health insurer or third party payor in the United States. It was believed necessary, from the federal government's point of view, to institute some type of review aimed at insuring that services paid for by the government were medically necessary and of appropriate quality. However, the utilization review programs of Medicare and Medicaid were fragmented and tentative.

Rather than establishing one utilization review program, three programs were developed paralleling the structure of Medicare and Medicaid. The first system for utilization applied to Part A of Medicare, that is, to the hospital insurance program. The original Medicare law required that each hospital establish a utilization review committee as a condition for participating in the program.

The second attempt at effective utilization review dealt with Part B of Medicare, that is, with supplementary medical insurance. Responsibility for evaluating medical necessity of physicians' services (which represent 90% of Part B coverage) was given to the insurance carriers.

Under Medicaid, the state plan had to include provisions to safeguard against unnecessary utilization.

There were then three programs, each with the same objective, which were administered and conducted by different groups. By 1969, a substantial body of evidence was developed in Congress attesting to the failure of these programs to achieve their objective. Some of the most apparent problems were

1. utilization review activities under Part A of Medicare were, generally speaking, of a token nature and ineffective as a curb to unnecessary use of institutional care and services;

2. performance of the carriers responsible for payment for physicians' services under Medicare varied widely in terms of evaluating medical necessity and appropriateness;

3. the law did not provide the Secretary of the Department of Health, Education and Welfare the authority to deal with providers and practitioners on an individual basis — i.e., he could not bar Medicare payments to those whose abuse of the program had been clearly established;

4. there was insufficient professional participation in and support of claims review by carriers and intermediaries and consequently there was only limited acceptance of their review;

5. the processes did not provide for an integrated review of all institutional and non-institutional services;

6. review activities were not coordinated between Medicare and Medicaid.

In August 1970, Senator Bennett, chairman of the Senate Finance Committee, introduced into the Senate an amendment, based on the Professional Review Organizations concept originaly developed by the American Medical Association but substantially modified, to establish Professional Standards Review Organizations throughout the U.S. Senator Bennett's amendment was modeled in several major respects on prototype review organizations which local groups of physicians had established in various parts of the country. This amendment, one among hundreds of changes, was included in Public Law 92-603 . . . the Social Security Amendments of 1972.

Following the passage of Public Law 92-603 implementation of the Professional Standards Review Organizations (PSRO) law began. Groups of dedicated physicians formed local organizations and contracted with the federal government to review medical care delivered to Medicaid and Medicare patients. In 1972 there were no Professional Standards Review Organizations functioning. By January 1981 there were 187 conducting reviews.

Physicians and staff of the PSROs had to battle hostility and opposition from many sectors. The American Medical Association encouraged opposition to them. Some state Medicaid agencies fought them in an attempt to retain authority, and thereby funding, for state review. Some hospitals resisted the system, which they feared would place a curb on income. Some physicians battled against anyone reviewing the necessity and adequacy of care delivered to their patients. Cries of interference between a physician and his patient were heard here and there. Fiscal intermediaries resisted relinquishing review to states and to PSROs.

But PSRO physicians and staff persisted. They patiently explained that the program was physician-directed; that it was designed to ensure that physicians make final determinations on medical necessity and quality based on criteria developed by their peers; that membership in the progam was open to all practicing physicians in an area; and that its review was objective, designed to correct only inappropriate patterns of practice.

As PSROs became more experienced they began to make better and more difficult decisions. Providers and practitioners who continued with inappropriate practice patterns after they were warned were sanctioned. Those whose behavior was aberrant but not abusive to the point of requiring sanctions were placed on pre-admission certification, consultation, and other approaches aimed at changing practice patterns.

During the next decade, physician organizations, by trial and error, developed techniques and acquired skilled staff support to accomplish review. The original concept of a battery of physician-developed standards of care against which all review decisions would be made was aborted in

From Lumberton Urology Clinic, 101 West 27th Street, Lumberton 28358.

the process of its birth. Instead, gradually a process of peer evaluation of inappropriate medical care evolved. With progressive sophistication, it became more effective in spite of opposition from our colleagues, from hospitals and the burdensome federal regulatory process which tried to dominate it.

As the cost of medical care increased and became the dominant force in the system, these organizations were increasingly measured, not by their impact on the appropriateness of care which they could affect but by costs over which they had virtually no control.

The present administration came to office with an avowed objective of federal deregulation in every area of our society and industries. Not only deregulation of airline, trucking, energy, and communications industries but also our health care industry. Regulation was to be returned to the forces of a free marketplace with competition to be the solution for all problems.

With present, socially significant and politically sensitive programs like Medicare and Medicaid in place, a pure free market is neither desirable nor attainable. With the Medicare program now costing more than a billion dollars every week, accountability became more pressing. Pressure began to mount, properly, from the Office of Management and Budget to switch the review process to the fiscal intermediaries where more regulated fiscal constraint could be exerted.

Certain congressmen, a majority in fact, more directly responsible to voters were reluctant to withdraw quality control of the system from the hands of the physicians. Under the leadership of Senators Durenberger and Baucus, legislation instead was drafted to reconstruct physician-directed review from a decade of experience. This new structure was signed into law with the Durenberger amendment to the Tax Equity and Fiscal Responsibility Act in the fall of 1982. The newly defined organizations were designated Utilization and Quality Assurance Professional Review Organizations.

Certain significant changes were made from the original Professional Standards Review Organization pattern. Instead of the original 200-plus areas, Professional Review Organizations (PROs) are conceived as basically statewide units. To encourage rather than thwart innovation the structure is less proscribed. They may, for example, be either non-profit or for-profit corporations. Funding is to be by a two-year objective-based contract rather than by annual grants. The cost is to be allocated directly from the Medicare Trust Fund as hospital cost under Part A rather than subjected to the insecurity of the annual appropriation process. Hospitals are required to cooperate in order to participate in Medicare payments. In the hope that the physician community would respond positively, they have been given exclusive bidding rights for the contracts — *but for only one year!* If no physician group comes forward with an acceptable proposal, the bidding process will then be open to any organization, including insurers or fiscal intermediaries, excluding only hospitals or other direct providers of care.

The specific duties of the PROs were not spelled out in the Tax Equity and Fiscal Responsibility Act but in the Social Security amendments, passed six months later in the spring of 1983. There was good reason for this vehicle.

There was great public debate and media coverage of whether or not the retirement age should be raised to 67 in 1990. There was emphasis on the political significance of bipartisan acceptance of these amendments proposed by a commission to save the Social Security System for all time, which incidentally had also been done only seven years before.

There was virtually no notice of the most significant change in the Medicare program since its enactment nearly two decades before — prospective payment system by Diagnosis Related Groups. Financing of care would no longer be allocated to hospitals on an open-ended cost reimbursement basis but by a pre-set price established by diagnosis. Equally remarkable was the fact that within six months this radical new approach was being phased into place.

With this new payment system and the resultant shift in financial incentives, the responsibilities of review organizations also shifted. Certain reasonable assumptions have been made regarding the effect of these new incentives. There will no longer be any cost-reimbursable incentive to keep patients in hospitals longer nor to do more tests and procedures. Review of length of stay and ancillary service review will now be accomplished intrinsically by the system not by the Review Organizations. Since payment will be made per episode of hospitalization, however, the indications for admission, re-admission and transfers within the system are not intrinsically controlled and must be regulated by the review process. The possibility of exceptional cases called "outliers" is acknowledged by the system but these must be certified as *bona fide* exceptions by the review process. Incidentally, the entire budget for hospital services by statute must be no more and no less under the Diagnosis Related Groups payment system than under the Tax Equity and Fiscal Responsibility Act "target rate" limits, and the outliers are to be no less than 5% nor more than 6% of the total.

The primary factor in the grouping process after establishing the principal diagnosis is the presence or absence of an operative procedure, either diagnostic or therapeutic. This may make a significant change in Diagnosis Related Groups pricing. Patients who receive certain invasive procedures therefore are to be selectively reviewed. Under the new system, payment depends not on the cost of resources consumed but on the diagnosis established by the medical record, which categorizes the admission to one of 470 specific payment groups. The validity of the diagnostic data on the record establishing this group must be verified by the review process.

Finally there is the intent that the new financial incentives will not compromise the quality of the care which Medicare beneficiaries receive. This quality review is also vested with the review process.

There are medically unjustifiable extravagances in the system at present. These are inevitable in a cost reimbursed system. That payment process is virtually at an end. Significant improvements in the efficiency of medical care delivery will emerge rapidly. There are serious concerns in many quarters about the potential effects of these efficiencies on the quality of the product, the outcome of medical care in the future. No one can assess these quality of care issues as accurately as the physician community.

These basically are the five responsibilities for which the

PROs will be contracting: 1. admission review; 2. outlier review; 3. procedure review; 4. Diagnostic Related Group validation review; 5. quality review.

Where are we today in this process? I indicated that the statutory authority for the review process predated by about six months the payment process. Contracting for the review process is of a much lower order of magnitude than implementing the payment process. The payment process is now about 70-80% complete. To date there have been no Professional Review Organization contracts signed. The reason is an interesting dichotomy within the administration. The Health Care Financing Administration, charged with the responsibility for implementing both programs, has been contending with every possible impediment which the Office of Management and Budget, another limb of the Executive Branch, could develop. The Office of Management and Budget is still hopeful of being able to eliminate physicians entirely from any control of the system and accomplish review with the more manageable fiscal intermediaries. After numerous technical delaying maneuvers, the requests for proposals by potential PROs were finally issued and except for certain waiver states those proposals were submitted April 27. The Health Care Financing Administration anticipates that contract negotiations will be completed and signed, and PROs will be in place by 1 July.

One basic precept inherent in the Durenberger proposal for PROs was to encourage innovation by review organizations. Contract objectives were to be individually negotiated to meet identified local circumstances. Delays generated by the Office of Management and Budget have now compressed the contracting time frame to a point where such individualizing is virtually impossible. Objective setting and the monitoring process by the bureaucracy were proposed to have a freedom of latitude also permitting innovation. Unfortunately, the request for proposals, when finally released, was highly proscriptive. The obvious intent of the Health Care Financing Administration is to require a consistency in contract proposals which will facilitate their review and approval by a simple check list procedure. Required objectives are rigid and designed more to develop national statistics which can be reduced to flip chart graphs for presentation at congressional hearings than to effectively assess the quality of care being delivered under the prepayment system. Battle lines are again drawn between PROs and the bureaucracy. The more things change, the more they remain the same.

We have looked at where we came from and where we are today. Now, where are we going with the concept of accountability by physician review? I believe accountability in our profession is overdue. There was a time when physicians were excused from accountability by a strange sort of mystical semi-divinity attributed to our profession. What we were able to do was more mystical than scientific, didn't make that much difference and really didn't cost much. We didn't have to be accountable. Nobody questioned. We would like to think we can still enjoy that immunity but we cannot. We are being questioned. Our accountability is being challenged. Not the least of these challenges is the rising flood of malpractice suits. I hate to see our professional accountability being relegated to our judicial system. We are being held accountable not only for quality but for cost. The new payment system incentives have resulted from a perceived lack of responsibility on our part to consider cost by those who pay for medical care for both public and private sectors. I am no more comfortable relegating our professional accountability to financial managers than to our judicial system. We are being held accountable, not only for our direct professional actions but for those we manage. It is estimated that 70-80% of the medical care resources consumed in this country are either performed or ordered by physicians. I do not try to deny that. I want that other 20-30%. Physicians should have the authority of all of the medical care our patients receive.

There was a time when patient care was exclusively a one-on-one doctor-patient relationship. We not only examined, diagnosed and prescribed but dispensed all the treatment there was. That time has long since passed. We are now supported by an enormous establishment of people and buildings and technologic equipment. We are more managers and decision makers in patient care but we still have the authority to determine the best course for our patients. There are many forces today striving to take away that authority. We cling to it tenaciously but if we are to keep that authority, we must be willing to accept the responsibility: accountability. In a profession, accountability takes the form of being willing to subject ourselves to the judgment of our peers. The corollary is a willingness to judge our peers. Both elements are necessary for professional accountability.

Today and in the foreseeable future we will be functioning in a system that is strange to us. We did not create the system but we have benefited from it and are part of it. Our primary responsibility is the care of our patients. We can only exercise that by retaining the authority over their care. If we use the system in that care, we must retain the authority over that system and we can do that only if we assure the accountability of that system.

There are dedicated physician groups all over the country who have organized PROs. I hope there are enough to do the job. They have trained a cadre of staff to assist them. This is not a volunteer effort but the providing of a medical service, and should be recognized and compensated as such. If previous patterns hold, and I see no reason they will not, the federal government will try to dictate the requirements and not want to pay what they are worth. That will be an on-going struggle. At present, the cost of review will be about three-tenths of one percent of the total Medicare budget which is not an unreasonable portion to devote to *quality assurance*.

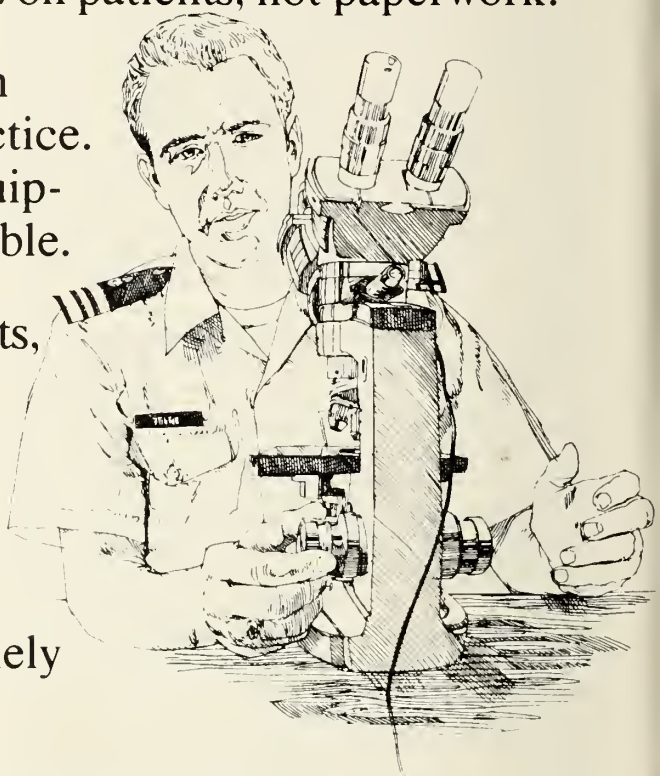
And quality assurance will continue to be the dominant concern of the physicians involved. With new financial incentives to reduce the consumption of medical resources, these quality of care concerns take on a new dimension. The purchasers of care, particularly the federal purchaser, will continue to demand less cost. There are costs that can be eliminated. There are some that can be reduced. Some will undoubtedly increase. Patterns of practice will change. There will be winners and losers. There should be.

It is my hope that we can maintain and enhance the integrity and credibility of our profession and retain the authority to manage the care of our patients. I see professional peer review as the mechanism to accomplish that objective.

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Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

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Adventures of a Latter-Day Carpetbagger

Leonard J. Goldwater, M.D.

ON January 31, 1984 some forty or fifty hardy souls braved a chilly wind to participate in a twenty-eight minute outdoor ceremony marking the opening of the Research Triangle Park office of the Occupational Health Service (OHS) of Duke University Medical Center. Present for the occasion were most of the individuals who had played important roles in the conception, gestation, birth and growth of OHS. Appropriately, E. Harvey Estes, Jr., M.D., Chairman of the Department of Community and Family Medicine at Duke, one of OHS's parents, presided over the proceedings. Others who spoke briefly were William G. Anlyan, M.D., Chancellor for Health Affairs at Duke, Ned Huffman, Executive Vice President of the Research Triangle Foundation, Susan Brown, M.D. of the Triangle Family Practice clinic and Lois M. Wysocki, Director of OHS. The ceremonial cutting of the ribbon to open the office was performed by Leonard J. Goldwater, M.D. who had the foresight to bring with him a pair of scissors large enough to do a proper job. (The "official" scissors were too small.) Incidentally, this snobbish gesture was characteristic of this Latter-Day Carpetbagger.* We shall hear more about those mentioned above, and about many others as the story unfolds.

In his remarks, Dr. Anlyan referred to his first encounter with the Carpetbagger which had taken place on or about January 2, 1967. The meeting had been arranged by Jay M. Arena, M.D. during a visit on December 27, 1966, the Carpetbagger's first contact with Duke. Thus it was Dr. Arena who opened the door. The Carpetbagger had established a beach-head in Durham. Earlier attempts to do the same in Chapel Hill had been unsuccessful.

Dr. Estes, too, dredged up a bit of history when he spoke of what had become known as "Goldwater's Folly." This refers to an abortive attempt in 1971 to set up a combined occupational and family medicine office in Parkwood, a residential community close to the Research Triangle Park. A pediatrician whose principal work was in Durham was then looking for someone to take over the lease on space he was renting. Included with the lease were the basic furnishings of a medical office, all at a bargain price. An added attraction was a clause in the lease whereby the owners of Parkwood agreed not to rent space to, nor to permit practice by, any other physicians as long as the lease was in force. It all looked too good to pass up, or so the Carpetbagger convinced Dr. Estes. But alas, the necessary staff and resources were not available and the project was abandoned after several months' rent had gone down the drain. Subsequent events, culminating in those of January 31, 1984, showed that the idea never died. It had merely lain dormant for a dozen years.

Also in the picture in the early days was another of the speakers at the opening — Ned Huffman who to some is Mr. Research Triangle Park. Following a visit from the Carpetbagger he arranged for the then Chairman of the Owners and Tenants Association of Research Triangle Park, Peter J. Chenery, to write to Dr. Estes on December 12, 1969 inviting him or his representative to meet with the Association to discuss ". . . the possibility of establishing some sort of occupational health facility to provide service to the tenants of the Research Triangle Park." The invitation was eagerly accepted, the meeting was held and shortly thereafter the first Research Triangle Park client, Burroughs-Wellcome Company, came into the fold.

The final speaker at the opening exercises, Lois Wysocki, entered the picture in 1982. There can be little doubt that if she had come to Duke earlier, the program would have been off and running several years sooner than was the case.

The Carpetbagger and His Early Days at Duke

Following visits to the Durham-Chapel Hill area in 1965 and 1966 the Carpetbagger decided that this would be an attractive place to operate following his retirement as Professor of Occupational Medicine, Faculty of Medicine, Columbia University in New York City. He was to be entitled to a sabbatical leave in 1967 and decided to make this a terminal leave and not return to Columbia at its expiration. He was anxious to attempt to write a book dealing with the historical aspects of mercury (quicksilver) and had obtained a two-year grant-in-aid from the Commonwealth Fund for this purpose. The folks at Duke graciously agreed to administer the grant and were perhaps pleased and relieved that no other commitment was required. They accepted the Carpetbagger's suggestion that he be designated a Visiting Scholar even though, as they said, this was a "first" for the Medical Center. A beachhead was now firmly established.

One requirement for a successful carpetbagger is to know what is going on in the place and field in which he is to operate. For the development of an occupational medicine program the ResearchTriangle Park appeared to offer fertile soil. Hairdressers and barbers usually are good sources of information, so the Carpetbagger decided to

From the Department of Community and Family Medicine, Duke University Medical Center, Durham 27710.

* Some who read this may recall from their studies of ancient history that it was the fate of southern nations and their cultures to fall prey to "Barbarians from the North." This epithet undoubtedly would be appropriate for some of the original Carpetbaggers of the 1870s. Its aptness in the present setting remains to be seen.

have his hair cut at the Parkwood Barber Shop, located just a few steps from where the new OHS office now stands. It was there that he learned about the medical office mentioned above and other matters of concern to him. It all looked encouraging. Potential client-companies were present in abundance.

Experience had taught, among other things, that when one embarks on a program of providing medical services in an organized way for groups of people, there are at least three questions that must be answered in the affirmative if one expects to be successful:

1. Is it legal?
2. Is it acceptable?
3. Is financial support available?

In this case *legalities* were chiefly concerned with the possible effects of a program that might earn a profit from the "sale" of medical services on Duke University's status as a tax-exempt institution. This was a particularly touchy matter since at that time the Internal Revenue Service was scrutinizing universities and other not-for-profit organizations. On the advice of counsel this possible danger could be avoided if a legally independent entity which would not claim tax-exempt status were set up to sell medical services. This was done in 1971 by the creation of Health Care Systems, Inc., as the agency which could make contracts with employers for providing a variety of health services. From the legal point of view it seemed not to matter that Health Care Systems was totally owned by Duke University and that it operated in a very close relationship with the Department of Community Health Sciences (later Community and Family Medicine). Profits after taxes, if any, from Health Care Systems were to redound to the benefit of the Department. A brochure prepared by Health Care Systems in March of 1979 noted that "Companies such as Burroughs-Wellcome, the National Institute of Environmental Health Sciences, the Environmental Protection Agency, the Research Triangle Institute, General Telephone Company of the Southeast, Liggett Group and General Electric are among the more than fifty firms relying on Health Care Systems for on-site and off-site medical services."

Acceptability involved several considerations. First there was the question of possible conflict with other interests and activities of the Duke Medical Center. This offered no problems since the services contemplated by the new program were in no way related to those already being offered at Duke. In fact, contacts and contracts with local employers for occupational health services could result in additional business for the hospital and for a variety of consultants.

Then there was the question of acceptability, or at least absence of opposition, on the part of the local private practitioners — the ever-present situation of "town versus gown." The fact that Dr. Estes had for some time been active in the affairs of the local and state medical societies facilitated a more or less painless resolution of this issue. Meetings were held with representatives of the medical societies at which the proposed program was explained, giving the local practitioners an opportunity to voice any objections. The physicians were asked whether or not any were currently providing occupational medical services to any local employers and if any were interested in doing so. This related to one of the missions of the Department of Community Health Sciences, namely, seeking out unmet medical needs and attempting to fill the needs. Some searching and even pointed questions were asked, but with consummate finesse Dr. Estes disarmed any potential opposition. The all-important question of acceptance by employers was one which only time could and would answer. About this, more anon.

Financial support for the program, at least in the early stages, was not a problem. A base of operations was provided by the Department of Community Health Sciences without appreciably increasing the overhead expenses of the Department. About the only cash outlay was for gasoline for the Carpetbagger's car as he went around calling on prospective customers.

A perennial problem in Occupational Medicine has been the provision to small enterprises of the same services that are economically feasible only to the largest through their own medical departments. An obvious answer is through collective action but this requires geographic propinquity of a number of small establishments and a nearby source of services. The Carpetbagger recognized that this combination existed between the Research Triangle Park and the Duke Medical Center.

The first local company to enroll in the program was a tobacco company which had not been solicited. This was in 1970. The company's physician was planning to retire and a replacement was being sought. This appeared to be a golden opportunity to get the program off the ground but it turned out to be something of a disaster. For one thing, the cost of providing the required services was grossly underestimated and secondly there was great difficulty in scheduling physician coverage by the limited staff available. In addition, one of the features of the plan that had made it attractive was the possibility of studying morbidity and mortality records of several thousand persons who were occupationally exposed to tobacco dust and who were given and who smoked liberal numbers of cigarettes. This was in the early days of the "cigarette scare" and appeared to be a golden opportunity to collect valuable epidemiological data. The company thought otherwise, perhaps not surprisingly. The final debacle came when employees reported to their supervisors that one of the Duke physicians was vigorously preaching about the dangers and evils of smoking. An escape clause was invoked and the contract was terminated in 1971.

The Carpetbagger had read Epictetus and remembered the words: "On the occasion of every accident that befalls you, remember to turn to yourself and inquire what power you have for turning it to use."[1] In this case, the use was that of the bellwether. It was most useful to be able to say to prospective clients that we were already providing service to one of the largest employers in the area. Even though the bellwether left the fold, other participants had begun to enter in increasing numbers.

While no large amounts of money were needed to initiate the service feature of the program two other aspects needed attention, namely, teaching and research. For these functions, no funds were at hand. In an effort to fill the gap the Carpetbagger established what he dubbed the Duke Mer-

cury Research Fund in 1970. The designation "Mercury" was chosen for several reasons. For one thing, the Carpetbagger enjoyed something of a reputation as an expert in the toxicology of mercury which in the early 1970s was "the pollutant of the month." Some of his associates credited him with having achieved the "summum bonum" of the alchemists, that is, turning mercury into gold. For the occupational medicine program this meant a source of income through consulting activities and from industries that were facing problems relating to mercury in the working and general environments. Paradoxically, there was less difficulty in obtaining contributions than in getting the financial officers of the Duke Medical Center to set up an acceptable mechanism for receiving and disbursing the funds. This obliged the Carpetbagger to resort to some slightly unorthodox tactics, such as a sit-in in the treasurer's office, to achieve his objectives. By the end of 1983 the Mercury Research Fund had received more than 500 contributions from about 50 donors for a total of approximately $300,000. While not an impressive sum, it aided in research at Duke and, through modest grants, in six other universities. More important, however, were the financing of fellowships and traineeships in occupational medicine at Duke, the purchase of books, expenses for attending scientific meetings and holding four symposia dealing with occupational and environmental toxicology. Assistance in handling the Mercury Research Fund was provided by Margaret F. Jones, who, in 1978, became Mrs. Leonard J. Goldwater.

It may or may not have been sheer coincidence that the Carpetbagger was associated with mercury. The god Mercury (Hermes to the Greeks) was not only the messenger of the gods and bearer of the caduceus but also the patron of commerce, gambling, cheats and thieves, to name but a few of his interests.

In the early days the program was pretty much a one-man show with part-time assistance from the late Dr. Albert Hathaway, whose principal duties lay in the Duke Student Health Service. It was obvious, however, that if the program were to grow, additional participants would be necessary. Occupational medicine has never been a specialty that attracted any significant numbers of young physicians. A few Duke medical students had been taking the elective courses that were being offered but the number was small and none showed any inclination to remain in the field. In 1971 there appeared on the scene one Woodhall Stopford, M.D. who called himself Sandy and, incidentally, is a nephew of former Dean Barnes Woodhall. He was undecided as to what he wanted to do after he had completed a one-year internship at Duke hospital and another year as Clinical Scholar. The Carpetbagger suggested that he consider occupational medicine but not until he had served a two-year residency in internal medicine in preparation for Board certification in that specialty. This requirement is based on the fact that a top-flight specialist in occupational medicine must be prepared to hold his own with some of the sharpest internists (and lawyers). So Stopford went off for a two-year medical residency and on his return to Duke in 1973 agreed to try occupational medicine for six months to see if it appealed to him. It took less than six months for him to make his decision and he has remained as a key person in the program. With the passage of time he has taken over more and more of the work of the aging Carpetbagger. Despite the heavy demands on his time he managed to earn the Master of Public Health degree at the School of Public Health of the University of North Carolina in Chapel Hill. This academic training is one of the requirements for physicians who wish to become eligible for specialty board certification in occupational medicine. These details on Dr. Stopford's career have been given in order to illustrate the demanding standards set for the professional staff of the Duke Occupational Medicine Service. This does not mean that all physicians in the program have completed such rigorous training. There is a place and need for others.

A giant step forward was taken in 1970 with the acquisition by the Department of Community Health Sciences of the Marshall I. Pickens Building. This modern, spacious edifice became a home for a number of the activities of the department, including OHS. For the latter this was particularly important since most of the clients of OHS had no medical facilities of their own. Thus the Pickens Clinic became the medical headquarters for a number of local enterprises as well as for the Employee Occupational Health Service for some 15,000 employees of Duke University, the largest single employer in the Durham area. The first full-time director of the latter, George W. Jackson, M.D., was appointed in 1982.

The work of OHS has never been limited to local clients. Before coming to Duke the Carpetbagger had established consulting relationships with a number of industries in various parts of the United States and abroad. Most of these have been continued and many more added. This work has provided a source of income as well as sites that have been used in the training of physicians and medical students. In addition, long-term observations on workers in various industries have provided material for research.

In a simple ceremony on July 27, 1981 the Occupational Medicine Program in the Department of Community and Family Medicine was given formal recognition as an integral element in the Duke Medical Center with David C. Deubner, M.D., M.P.H. as Director. At that time the Carpetbagger was presented with a handsome chair. It may have been the hope of the donors that he would use the chair to take a back seat, but this he stubbornly refused to do. A plaque affixed to the chair contains the words: "To Leonard J. Goldwater, M.D., C.O.B." The last three letters stand for "Crusty Old Bastard," a title the Carpetbagger wears with pride.

Another important step in building the professional competence of OHS was taken in 1981 when Leon Golberg, M.B., B. Chir. joined the group. Dr. Golberg, a toxicologist and scholar with an international reputation and a distinguished career in England and in America, had been Founding President of the Chemical Industry Institute of Toxicology (CIIT) in the Research Triangle Park. He resisted an invitation from CIIT to continue there upon completion of his five-year contract and decided instead to accept a post at Duke in OHS. This choice was made in the face of many attractive offers elsewhere. He has made and continues to make important contributions to the teaching, research and consulting activities. His presence has helped to cement relationships between Duke and CIIT.

Teaching and Training

Starting in the early 1970s elective work in occupational medicine was offered to undergraduate medical students but not many were attracted to these courses. It was never entirely clear how many of those who signed up did so because of genuine interest or because the hours and credits suited the convenience of the students. In either case a dozen or so Duke graduates left the medical school with some idea of what Occupational Medicine was all about.

In 1976, Patrick R. Conner of Burlington, North Carolina, then a third-year medical student, chose to take elective work in Occupational Medicine. He later (1984) confessed that this had been a matter of convenience but he became so interested in the field that in his fourth year he spent a full two-month rotation at an occupational health teaching center in a distant city. After completing his internal medicine residency he returned to Durham and supported himself and his family by working part-time at the International Business Machines Company in the Research Triangle Park while earning his Master of Public Health degree at the University of North Carolina and attending the weekly OHS seminars. He may be considered to be one of the first two full-fledged products of the Duke Occupational Medicine training program. Conner was succeeded in 1978 by William B. Bunn, III who, following his elective studies, was awarded a Mercury Research Fund Fellowship for nine months while awaiting the start of a medical residency at the Duke Medical Center. Bunn, incidentally, had taken the combined M.D.-J.D. curriculum at Duke and later earned the Master of Public Health degree at the University of North Carolina in Chapel Hill. Upon completion of this rigorous program he was appointed on January 1, 1984 to a full-time position in the OHS. Of some significance is the fact that during Bunn's medical residency he was permitted to spend a certain amount of his time with OHS. A part of this time was devoted to exploring and developing relationships between the medical service at Duke Hospital and OHS, particularly in two-way consulting activities. This arrangement was formalized in March of 1984 when Bunn was given a joint appointment on the medical service of Duke Medical Center. Like Conner, Bunn is a native of North Carolina, having grown up in Raleigh.

Short-term fellowships similar to that held by Dr. Bunn have subsequently been given to several recent graduates of the Duke Medical School and continue to be available.

Between 1979 and 1983 the teaching program was kept alive largely through the devoted efforts of John W. Cromer, Jr., M.D. who continues to play a role along with Dr. Stopford.

UNC and OSHERC

Although the Carpetbagger had been shunned at the University of North Carolina in Chapel Hill when he first arrived in the South, he later was offered and accepted a teaching appointment in the School of Public Health. This was in 1970 and it marked the beginning of a relationship between UNC and the Duke OHS that was to become increasingly close. The first UNC faculty member to become involved with OHS was Ted Williams, an industrial hygienist, who provided valuable assistance in the days before OHS employed its own industrial hygienist, Gary Shaver, in 1979.

Additional ties between the sister institutions evolved, starting in 1977, with the establishment of a regional Occupational Safety and Health Educational Resource Center (OSHERC). North Carolina State University in Raleigh was also involved in this activity. The North Carolina OSHERC program was one of about a dozen that were organized in various parts of the country to take advantage of Federal funds administered by the National Institute of Occupational Safety and Health (NIOSH), the principal purpose being to provide continuing education for individuals concerned with various aspects of occupational health. Primary administrative responsibility for OSHERC was assumed by the School of Public Health at UNC which had a strong program in industrial hygiene but was weak in medical aspects. The Duke OHS provided physicians and N.C. State covered safety engineering and related areas. Physicians from the Duke OHS have been major participants in many of the OSHERC activities including two annual week-long teaching "institutes" for occupational health professionals. Weekly seminars attended by students and faculty represent another joint effort of the three Triangle universities. These sessions are open to all interested persons and attract representatives of local industries, health officials and others. In 1984 NIOSH rated the North Carolina OSHERC program as the best and the Duke medical component also as the best in the country. It was gratifying that the high standards of the Duke OHS should have received this recognition.

Residency Program

As the occupational medicine program grew it became apparent that a possibility existed for it to become a major center in its field. One feature would be an accredited residency training program designed to prepare candidates for certification by the American Board of Preventive Medicine (Occupational Medicine). One of the requirements, an academic year in a school of public health leading to a Master's degree, was readily arranged through the School of Public Health of UNC. Resources of OHS were suitable for the clinical and practical experience necessary to meet the Board requirements. Conditional approval was granted by the Residency Review Committee in 1981 and full approval in 1984.

Some question exists as to who should be given the distinction of being the first resident physician. As mentioned above, Dr. Bunn served a part of his residency in the OHS by arrangement with the Department of Internal Medicine where his principal appointment lay. First to enroll as a resident for the full two-year term was Gary N. Greenberg, M.D. who served from July 1982 to June 1984. At the time of this writing (March 1984) selections are being made from among several dozen applicants for the next group of residents. Preference is being given to those with a strong background in Internal Medicine.

What of the Future?

The literature contains conflicting views of the usefulness of the past in predicting the future. Edmund Burke (1728-1797) said that "You can never plan the future by the

past,"[2] and Adelaide Ann Procter (1825-1864) of Lost Chord fame declared that "The past and the future are nothing."[3] On the other hand Gottfried Wilhelm Leibniz (1646-1716) has been credited with saying that "The past is pregnant of the future" or some German words to that effect. It is not clear whether or not this view was one of the reasons why Voltaire (1694-1778) made Leibniz a particular target for ridicule in *Candide*. Voltaire notwithstanding, our brash Carpetbagger chooses to accept Leibniz over the other experts on prognostication.

There are several reasons for predicting that the Duke OHS will continue to grow. Not the least important of these is that the Carpetbagger is no longer the only player in the game. A team of high calibre has been assembled, they know what to do and how to do it, and recognition of their capabilities is gaining wide acceptance. Nationwide, concern with occupational health and related areas such as environment and hazardous wastes is growing. There is, of course, a certain amount of competition, but few individuals or groups can offer the resources, quality, experience and professional competence that has been assembled at Duke. (If this sounds like a "commercial" it is intended to be just that.) The large number of applicants for training in the Duke OHS program is but one evidence of this group's high reputation.

Among plans currently under consideration is a proposal for a Center for Toxicologic Medicine. To quote from a document prepared in August 1983, "This center would be multidisciplinary and would specialize in the highly sophisticated clinical evaluation of persons suspected of having effects of toxic exposures and the integration of that evaluation result with investigation of the toxic exposure to arrive at judgments of their interrelatedness." In essence this would be an extension of one of the traditional roles of Duke Medical Center in dealing with difficult or complicated medical problems.

The future looks bright. The Carpetbagger apparently knew what he was doing when he moved into North Carolina.

Postscript

"The living legend . . . is a vulnerable creature. His life's work completed, appraised, classified, he alone remains at large, uncertain and unpredictable. . . ."

Kevin Brownlow
The Parade's Gone By

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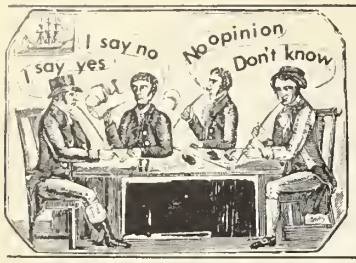


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Ideal Work Week

Eugene W. Linfors, M.D., editor

Will doctors of the next generation be less productive because of a trend toward the shorter work week? Is there an ideal work week for the practicing physician?

From Dr. John R. Chambliss, an internist in Rocky Mount.

These are two interesting and provocative questions. Most of us equate production with money. If you will allow me to do so, I would then ask the first question in different words, namely, "How can I have more time off and make the same or more money?" I find the priorities of the younger generation somewhat changed from those of we older physicians. As usual, I think that they are correct. There is little merit in continuing the old customary 60-hour week. I do believe physicians deserve more time for their families and recreation and I think this will contribute to their efficiency. To have a shorter work week, however, and maintain production or income is going to be difficult. This only can be done by more efficient utilization of one's working hours (when do you go to all those hospital committee meetings?) or by raising fees. More and efficient use of time means greater dependence on ancillary help (and thus more employees and increased overhead) and having the physicians do only those things physicians alone can do. I find young physicians most willing to work long hours. They do wish to work a shorter work week and wish some reasonable degree of protection from night work by cross-coverage. I do think they are quite willing to work longer days and less days a week.

Raising fees, which are probably too high now, in the current environment is unacceptable. I believe that the super specialists can obtain these two goals, namely a shorter week and the same or greater pay. I do not think those of us in primary care can do so. It is quite possible when the "doctor glut" fully materializes we may have a shorter work week whether we like it or not.

I do not know the answer to the question, "What is the ideal work week for physicians?" I have great fear that external factors are going to determine this for us and we may have a complete change in our life style. Our hospitals are struggling to survive under DRGs. If we are going to survive, our hospitals have to survive. Can our hospitals afford to close down operating rooms and supporting services two out of seven days? I tend to doubt that they can do this and survive DRGs. If the hospitals are going to work seven days a week, then the physicians are going to have to work seven days a week. This can only be accomplished by organized cross-coverage and a change in the pattern of a physician's life style. It may be that our "weekend off" in the future may be days in the week other than Saturday and Sunday. Perhaps the "doctor glut" will help solve the problem of the shorter work week but I do not see how it can maintain production (money). The same pie will simply be cut into smaller pieces.

It will be only in rare instances that the goals of a shorter week and maintenance of production can be achieved. Perhaps in the future we will learn that more time off is worth the price.

From Dr. Theodore R. Clark, a psychiatrist in Pinehurst.

In response to the above questions, some doctors undoubtedly will be less productive, other doctors will leverage their time with computers and ancillary personnel. "Is there an ideal work week for a resident physician or practicing physician?" Yes — 40 hours.

From Dr. Dan Constien, chief resident in family medicine in Greenville.

When asked whether the doctors of the next generation will be less productive because of the trend toward a shorter work week, I wonder what is meant by "productive." Does it mean the number of patients seen, the number of surgeries performed, the amount of money made, or does it reflect the quality of care that is rendered? As a resident in Family Medicine, I often feel like the woman with 13 children who when asked if she had enough time to take care of all her children replied that when she had only one child she didn't have enough time.

So many times, I have wished that I had more time — time to counsel an anxious or depressed patient, time to review nutrition, safety, or stress reduction with a patient who comes in for other reasons, time to work in the walk-in patient without causing undue waiting time for the others, or time for myself — reading or recreating.

Is there then such a thing as the ideal work week for a resident or practicing physician? The answer is an individual one based on the quality of care one wishes to give, the quality of life one wishes to live, and for most, time will always be too short.

From Dr. Conrad Fulkerson, a psychiatrist in Durham.

With productivity in medical practice defined very basically as the effective and efficient evaluation and treatment

of health status and/or problems of individuals, I believe that the physicians of the next generation will be equally or even more productive than their predecessors despite a shortened work week.

The factors that will influence physicians and their patients in the years to come are so numerous, broad ranging, and varying in their potential effects that the shape of future medical practice, including level of productivity, is extraordinarily difficult to predict. Particularly confusing are factors somewhat beyond the traditional biomedical sphere such as the overall economics of medical care; changing expectations, lifestyle, and sophistication of both patients and physicians; and the revolution in information storage, processing, and transfer (even as I write this opinion on a word processor). I do not pretend to have considered and weighted all of the possible influences and my contention of equal or greater productivity may be as much a personal attitude reflecting my general optimism (looking forward to a few days away) as much as anything close to an informed prediction. Nevertheless, it seems to me that we are generally working smarter, more effectively, and more efficiently in most areas of life, including medical practice.

I believe that there are some particularly important determinants in this trend toward greater productivity in medical practice. The "slack" in medical practice of past years in terms of repeated tasks performed with unnecessary investment of time and energy, data "hand carried" in office and hospital, and record keeping systems akin to those of scribes of biblical times (to mention but a few examples) is being taken up and this will continue at an advancing rate. Second, demands from consumers and financial intermediaries in medical care are clearer, more consistent, more informed, and less ignored than ever. Finally, we seem to repeatedly rediscover just how work may expand to fill time available in which to do it and seem to gradually become less tolerant of burdening ourselves unnecessarily.

In my own practice of outpatient psychotherapy-based psychiatry I have had, against the dreary background of the psychiatrist's famous compulsive adherence to routine of schedule and procedure, some opportunity to observe myself more carefully than in the preceding five years during which I seemed to be always running about while engaged in training and then brief practice of internal medicine. A lesson that I have learned (and relearned over and over) is the subtle effect of fatigue on my capacity for focus of attention, mental processing of information, and experience of my own affective state. With the consistency of seeing the same individuals session after session in the same setting dealing with aspects of the same issues I note a significant difference in my functioning depending upon whether I am stressed, overworked, or recently vacationed. The fact that I can conduct apparently passable psychotherapy in a relatively fatigued state sometimes frightens me when I find just how much more effective I can be when rested. My productivity (my capacity to make some usable sense out of the material that the patient is presenting at the time such that the patient himself may be better able to think, feel, work, etc.) seems highly dependent upon the amount of work I attempt to do in any given period of time and the opportunity for such serially controlled experiments (working in simple and consistent circumstances both rested and fatigued) has convinced me that many times both in my training and in my practice I have worked on the "down side of the Starling curve" in that my continuing efforts sometimes become progressively less efficient the more I "stretch" myself.

Whether such observations are transferable to the general practice of medicine or to other individuals could be debated but I submit that the activities of receiving and processing information and then making and implementing decisions based on that processing are central to thoughtful medical practice. I conclude, based on these observations, that (1) mental and/or physical fatigue significantly affects my work and "productivity"; (2) though the diminution in my effectiveness seems somewhat linear with cumulative fatigue, there are points at which attempts at continued work seem to more rapidly decrease productivity; and (3) with the fatigue occurring gradually and with frightening subtlety, I do well to give attention to the amount of work I schedule for myself and the commitments I make for any given period of time.

Given the peculiar aspect of human frailty that seems to distort our ability to know ourselves with progressive fatigue, "burnout," or intoxication, I believe that there is a case for attempting to determine and implement a personal "ideal work week." There are a great many variables that figure in such a determination and it is difficult to consistently closely approximate this ideal in practice week after week. I do believe, however, that most individuals can, with some reflection, introspection, and possibly feedback from others in their environment make some determination of their own capacity for productive work within a given period of time. Scheduling and structuring time away from work for activities unrelated to work are critical for most physicians to achieve this since most of us relate to idle time the way that nature deals with a vacuum. The physician, surrounded today by remarkably complex and diverse instruments, is still primarily his own most important tool and, as such, deserves the finest care, certainly equal to the care given today to key business executives or athletes.

From Dr. William P. J. Peete, a surgeon in Durham.

In my view doctors of the next generation will not be less productive because of the trend toward a shorter work week. There will be greater efficiency because of advances in technology such as NMR and in the use of technology. Undergraduate and graduate students are at least as intelligent as past ones, and continue to be highly motivated to excellent patient care, teaching and research. I think the doctors of tomorrow will find ways to tilt at fewer windmills, those impossible situations where we spend so much time and money and produce so little, sometimes only grief. This will come about because of wise patient wishes, greater soul searching by physicians and financial pressures to reduce medical costs. Financial pressure will also make research more efficient. Actually a shorter work week in itself may create greater productivity: the heart rests more than it works. The great surgical producer William S. Halsted was notable for three and six month vacations. For the problems which face them, the doctors of tomorrow may indeed find solutions in a shorter work week. If not, despite the trend toward a shorter work week, they will

spend the time needed to solve them.

I doubt there is an ideal work week. There may be an ideal work goal. Dr. Richard Cabot, well known for beginning clinico-pathologic conferences and social service, felt strongly that full development of a physician required he learn to and continue to work and play, to love and worship in a balanced way according to *his* capacity. Dr. James T. Cleland once told a colleague at Duke University that his colleague's sin was not that he loved the University but that he worshipped it. For the physician it may be important to substitute medicine for University to reflect upon false Gods. I think the ideal work week will vary with the time in one's life and his capacity and needs at any one time, not just residency and practicing physician. For example some need only four hours sleep. Some find play and love in work. Even so, the tendency for the modern physician and the system in which he works is to overfocus on work; to permit neglect of play, love and worship, and to suffer because of both. If one works with Cabot's convictions and Cleland's nuance in mind, then a successful work week can vary between less than forty to more than a hundred hours a week.

From Dr. William B. Tarry, Jr., a family practitioner in Oxford.

In company with most other productive groups of one kind or another, physicians for many years have pursued means of shortening their working hours and securing more leisure time — the pursuit always modified by reluctance to take a cut in income in order to do so. Group practices have multiplied in number and continue to grow in size. Emergency rooms have provided more and more acute (and even chronic) care outside regular working hours. Establishments providing 24-hour care for acute illness or "minor" trauma have burgeoned in urban areas. Paramedical people now provide a significant amount of medical services.

Most of this change is the result of changing public demand rather than a concerted physician effort to shorten working hours. Patients are ever more knowledgeable, confident, and secure in asking for what they want. Much innovation and change in medical care will result from increasing patient independence. More emphasis will be placed on what they want rather than what we think they need. And it is about time.

Will these changes and pressures reduce the productivity of the new generation of physicians? I don't think so. Physicians have not changed — their public image has. The new group is composed of exceptionally intelligent, decently motivated and well trained professionals whose education has progressed with the times. There are those among them who will choose the regimented stable conditions and regular hours of emergency rooms, acute care centers, and institutional work as well as the less patient oriented specialties. Large numbers also will eagerly accept the challenge, the responsibility, and the privilege of providing comprehensive medical care. They will find new ways to do more in less time but they will not be less productive. They will charge more but it will be worth the cost.

We live in a small town of about 10,000 with a 65 bed general hospital and serve a population area of perhaps an additional 15,000 people. The hospital staff includes six FP's (our group of two, one group of three, and one solo), two independent internists, one OBGyn and two general surgeons who are partners. All are in full-time practice, hospital and office. Our average work week is about 65 hours which includes administrative and staff duties as well as patient care. The accuracy of this figure is open to some question because some of these fellows sometimes can't tell the difference between what they do for a livelihood and what they do for fun. If you ask their wives for an estimate of their spouse's working time, the number of hours is almost invariably longer. I don't know what this means. None of us feels overworked. Although there is much wistful talk of "more time off," nobody seems to be doing much about it except for the trading of calls between individuals and the regular time-sharing within groups. A new physician moving into this area should expect to devote at least as much time, perhaps more, to establishing and maintaining a practice, whether in a group or solo.

Life and medicine are becoming no less complex. House officers should not expect to clock less time in their introduction to the profession; 90-95 hours weekly as a minimum does not seem unreasonable.

• EDITOR'S NOTE: As I read our sample of opinions I hear both optimism and a little uncertainty. By more efficient use of such aids as word processors and new diagnostic tests we can be more productive in fewer hours. However, external factors may determine our work week as much as we ourselves do. I don't hear any philosophical objection to a shorter work week.

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Features for Patients August 1984

Communication for the Speechless Person

Jennifer Horner, Ph.D.

The purpose of this article is to describe the role of technalagy in cammunicating with adults wha because of injury ar disease have partial or complete lass af speech. We begin with same definitians.

Neuralagic prablems interfering with speech may accur suddenly or they may pragress slawly aver time. The major types af cammunication problems resulting fram neuralagic damage are *dysarthria* and *aphasia*.

Dysarthria is a speech problem resulting from damage to the central nervaus system ar peripheral nervous system that causes muscles producing speech to become weak, slow, or incaardinated. The quality af speech is likely ta be altered when muscles important to breathing, voicing, and maving the saft palate, the tangue, and the lips are impaired. Peaple with dysarthria are unable ta speak normally because af impaired muscle functian.

Aphasia is a language prablem resulting fram damage ta the central nervous system, usually the surface of the brain. Aphasia may invalve problems understanding what athers say, prablems expressing ideas with wards and sentences, ar prablems reading and/ar writing.

Thus bath dysarthria and aphasia result fram damage ta the nervous system. Dysarthria is a speech prablem that affects haw quickly, evenly, ar clearly we speak. Aphasia is a language prablem that impairs aur ability to understand ar express in wards and sentences. In neither dysarthria nar aphasia *per se* is the person necessarily confused. In bath dysarthria and aphasia the degree of the communicatian problem spans a braad and camplex cantinuum: the prablem may be mild, moderate, severe, or prafaund. If speechlessness occurs, the prablem may be described as prafound. Some speechless individuals have the patential for cammunicatian by means other than speech and can be helped by madern technology. The technical term far these cammunicative systems is "augmentative cammunicatian systems."

From the Department of Surgery, Divisian of Speech and Hearing Disorders, Duke University Medical Center, Durham 27710.

Incidence and Prevalence

Dysarthria. About 14 of every 1000 persons in the papulation have same farm af neurologic disease.[1] Each year appraximately 8 persans af 1000 in the general papulatian are newly affected with a neuralogic disease. The ages at which progressive neurologic diseases are likely ta accur differ. For example, multiple sclerasis usually begins between 20 and 40 years; Parkinsan's disease, after 50; and amyatraphic lateral sclerosis, between 40 and 60.[1]

Aphasia. The major causes of acute ar sudden anset neuralagic injury are head trauma and strake. Each year, appraximately 10 of 1000 Americans will sustain a seriaus head injury, usually as a result af autamobile accidents. Thaugh head injury may occur at any age, young adults are mast often the unfartunate victims.[2] Unlike head injury, strake is related ta age. Under the age of 35 stroke is rare; under 45, infrequent. Amang persans 45-54 years, strake occurs in 1 of every 1000; amang thase 55-64, abaut 4 af every 1000; amang thase 65-74, 9 af every 1000; and among thase over 75, 30 of every 1000.[3]

Rehabilitation

The number of persons with either dysarthria ar aphasia is unknawn. According to an HEW report, of every 100 people who survive a stroke ". . . 10 will be able to return to work virtually without impairment, 40 will have mild residual disability, 40 will be so disabled as to require special services, and 10 will need institutional care."[3]

The cancept af rehabilitatian is not a new one but the canvictian that "rehabilitation helps" is extending beyond health prafessianals ta the general community. Several publicatians fram the National Institutes of Health[4-6] describe developments in biomedical, sacial and behaviaral research that help us appreciate the breadth and importance of human services and delivery systems. The gaals af angaing federally funded research and the gaals af existing rehabilitatian programs are compatible. Far persans with an acquired

neuralagic problem, the gaals include: 1) ta minimize the degree ta which an impairment becames a disability, 2) to reduce and prevent dependency, 3) ta raise the expectations af the patient, family and athers in the patient's enviranment, and 4) ta meet these abjectives by praviding oppartunities for change. While the speech/language pathalagist is usually the persan directly invalved with rehabilitatian af the cammunication-impaired persan, many other prafessianals cantribute ta the greatest passible rehabilitatian af the patient. Depending on the specific setting, the rehabilitatian team may include the neurologist, orthapaedic surgeon, other physician, rehabilitation nurse, physical therapist, psychiatrist, neuropsychalagist, sacial warker, vacatianal rehabilitatian caunselar, and prasthetic, arthatic and enviranmental cantral specialist. The multidisciplinary rehabilitatian setting is ideal for the speechless person wha has potential for using an augmentative cammunicatian system.

Augmentative Communication Systems

Follawing head injury ar strake, or during a pragressive neuralagic disease, an individual may be unable ta cammunicate orally and sa need technalogic help. The persan with same residual speech may use aids ta augment speech; the persan wha is speechless will use such aids ta replace speech. A variety af factars influence what type af augmentative cammunicatian system is mast suitable far a speechless individual. These factars include physical ability, language ability, and the ability ta think.

Physical Ability. Same individuals with neuralogic disease causing them ta be speechless may have full use af their arms and legs; others may have limited use; athers may have na use. The individual's ability ta adapt ta ar campensate far a physical disability may depend an his respanse ta physical therapy and/ar the use af braces ar supparts. The mast physically impaired persan may have to rely an residual mavement abilities such as head turning and tilting or eye blinking. A persan's ability to mave a bady part valuntarily and cansistently, and the range, strength, accuracy and speed af mavement are impartant considerations.

Language Ability. It is necessary far the augmentative cammunicatian system user ta have same language ability. A persan with a prafaund dysarthria and a significant degree of aphasia will have ta rely on the most basic af communicatian aids. In contrast, the persan with a prafaund dysarthria and na aphasia is a goad candidate ta use a camplex cammunicatian aid.

Ability to Think. The thought pracesses underlying cammunicatian depend on adequate attentian, perceptian, memary, behaviaral self-cantral, and a wide variety af other factors. The simplicity ar camplexity of an augmentative cammunication system depends ta a great extent an the individual's general intellectual state and an the mativatian ta use the system pravided. The Rancha Las Amigos Haspital[2] has develaped an extremely useful appraach to assessing the cagnitive status of head-injured adults. Their "Levels of Ability ta Think" describes 8 levels af functianing. Level 1, the lawest level, describes the patient who appears to be in a deep sleep and completely unable ta respand. Level 8, the highest level, describes the patient wha is alert, able ta learn, independent in hame and cammunity skills, etc. The patient at this highest level is usually belaw his pre-injury level but is functianal sacially,ematianally and intellectually.[7] In my experience, a head-injured patient must be functianing at least at Level 6 and ideally at Level 7 ar 8 in arder ta use an augmentative cammunication system.

Once the several facets af the speechless persan's capabilities are determined, the speech/language pathalagist can select the appropriate technalagic system. There are three braad levels of difficulty: 1) basic, 2) intermediate, 3) camplex. The successful use af an augmentative cammunication system depends an an



Figure 1. Three basic augmentative communication systems: Picture board; picture communication ring (illustrations from *Talking Pictures*, Crestwood Co.); alphabet board.

oppropriote motching of the copobilities of the user with the complexity of the system. For this reoson, it is importont that o troined professionol conduct on evoluotion ond observe the use of the system before the system is fully constructed or purchosed. The professionol consultont is olso responsible for troining the user ond other importont persons in the user's environment, os well os colling on other professionols who con assist in odopting the system to the specific requirements of the user. The following review of systems is selective, to give the reoder an ideo of the types of systems ovoilable. Other opproaches ond systems are ovoiloble (see oppendices).

Basic Augmentative Communication Systems ore typically designed for the broin-injured odult who is speechless due to o combinotion of dysorthrio and ophosio. The obility to perceive complex visuol moterial (such os printed words) moy be impoired, or the obility to use o wide ronge of vocobulory words moy be impoired.

Figure 1 shows three bosic ond eosily constructed ougmentative communicotion systems: o picture communicotion boord, o picture communicotion ring,[8] ond on olphobet board. They require some monual dexterity, such os pointing, ond they ossume thot the user is oble to select reliobly from the pictoriol or olphobet disploy. All hove the odvontoges of being light, portoble ond virtuolly cost-free. The olphabet boord hos the advontoge of ollowing the user to communicote o wider range of ideos, but of course the user must be able to spell. A pointing boord comprised of orgonized lists of frequently used words con olso be constructed.

The ZYGO ougmentotive communicotion system shown in figure 2 is o 16-item disploy that con be reodily individualized, either with printed words (os shown) or pictures. The ZYGO is suitoble for the speechless potient who has limited use of his orms. The user of o ZYGO system scons the boord by using o remote switch ond stops the sconning light ot the item he wishes to communicote.

Figure 3 shows o voriety of switches thot ore used to odopt to the needs of the individuol user who wishes to octivote o system like the ZYGO. Other odoptotions for bosic communication systems include light beams or pointers stropped to the user's heod. For the user who desires o brooder "vocobulory," o ZYGO with o 100-item ponel is ovoiloble.

Intermediate systems ore relotively brooder in their opplication, hove o more complex letter/word or picture disploy, ond/or use on ortificiol voice. The user must hove o foir degree of longuoge obility — including the desire to communicote o wide ronge of ideos — to use these intermediote augmentotive communicotion systems effectively.

One type is the Canon Communicotor (figure 4). This is a modified olphobet board, with letters orgonized by the frequency with which they ore used in the English longuoge, olong with numbers ond punctuotion morks. An overloy is provided for the potient who hos difficulty with very fine motor coordinotion. An ottroctive feoture of the Conon Communicotor is the use of o tope on which the printed messoge is permonently recorded.



Figure 2. A ZYGO communicotion boord with light sconner (ZYGO Industries, Inc.)



Figure 3. Adoptive switches for the ougmentotive communicotion system user who is physically limited.



Figure 4. A *Conon Communicotor* with battery pack ond overloy (Telesensory Systems, Inc.)



Figure 5. Two artificial voice systems: *Special Friend* (Shea Products, Inc.), and *Vocaid* (Texas Instruments).

The three ortificiol voice systems selected for illustrotion (figure 5 ond 6) use touch-sensitive panels to activote them. They vory in the complexity of the visuol disploy but are similor in thot words (or pictures), sentences, letters, ond numbers moy be selected. They shore the speciol feature thot messoges ore conveyed by woy of o synthesized (electronic) voice.

Complex ougmentotive communication systems ore designed for the person who is physicolly limited but cognitively ond linguisticolly normol or neor-normol. Complex systems require good leorning ability ond motivotion ond ore usuolly computerized ond therefore more difficult to operote. Severol systems include the feature of on ortificiol voice. Though usuolly more expensive thon basic ond intermediote systems, complex systems offer the distinct odvontoge of ollowing the speechless potient with good language not only to communicote but also to leorn ond creote.

Prentke Romich Compony hos produced o wide voriety of complex communicotion systems, some of which ore shown in figure 7. They hove devoted reseorch funds to the compilotion of o comprehensive chort summorizing the mony feotures of 44 commerciolly ovoiloble oids manufoctured by both Prentke Romich ond other componies.[9] (See oppendices.)

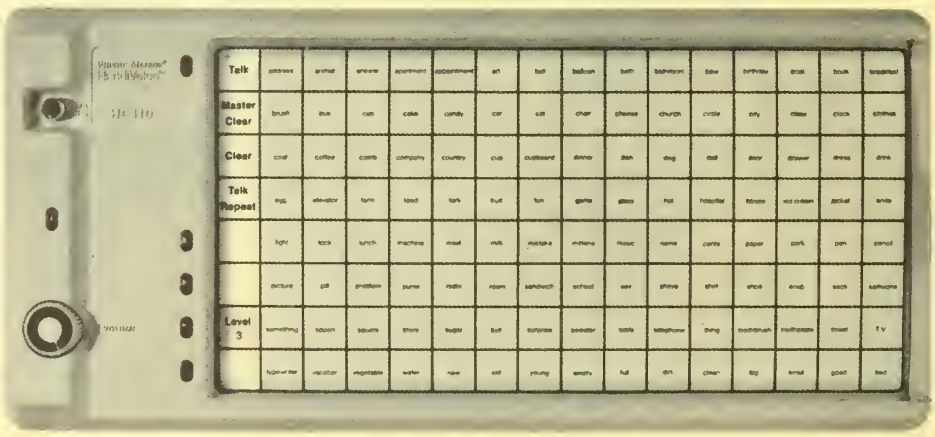


Figure 6. The *Handivoice 110* artificial voice system (Phonic Ear, Inc.)



Figure 7. A variety of complex augmentative communication systems (Prentke Romich Company).

Summary

The need for augmentative communication systems is very real and the need is being met. In the past decade, remarkable innovation has occurred in the development of a wide variety of systems. The speechless person with both ability and motivation can learn to communicate again.

Acknowledgments

I oppreciote the help of Edward B. Mostin, Medicol Photographer, Duke University Medicol Center, and Rick Block, Sales Representotive for Prentke Romich Company.

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Appendices

Special Publications

Communication Outlook: A Publication of the International Society for Augmentative and Alternative Communication (ISAAC). Artificiol Longuoge Laborotory, Computer Science Deportment, Michigan Stote University, Eost Lansing, MI 48824-1042. (Annual dues and 4 issues of mogazine: $12.00.)

Features of Commercially Available Communicotion Aids. Prentke Romich Compony, 8769 Township Road 513, Shreve, OH 44676. (Send $1.00 for chort.)

Manufacturers and Names of Augmentative Communication Systems

Abbey Medicol, 8004 Westchester Pike, Upper Dorby, PA 19082. ("PMV")

American Communicotions Corp., 180 Roberts St., East Hartford, CT 06108. ("Am-Com I")

Communicotions Research Corp., 1720 130th Ave., N.E., 8ellevue, WA 98005. ("Omni Communicator, Model 1" and "Omni Communicotor, Model 2")

Computers for the Physically Hondicopped, 7602 Tolbert Ave., Huntington 8each, CA 92647. ("TIM")

C-Phone, 553 Wolfner, Fentin, MI 63026. ("Miniphane" and "Pocket Phone II")

Educotianal Microcomputer Systems, 1 Cleor Spring, Irvine, CA 92715. ("Communi-Mote")

J. A. Preston Corp., 60 Page Rd., Clifton, NJ 07012. ("Scon 100 Communicotor" ond "Scon 40 Communicotor")

Krown Research, Inc., 6300 Arizono Circle, Los Angeles, CA 90045. ("Porto-printer Plus")

Micro Communicotion Devices, 12388 Priscillo Lone, Los Altos Hills, CA 94022. ("Video-Com II")

N.A.P. Consumer Electronics Corp., 159E. Union Ave., Eost Rutherford, NJ 07073. ("Odyssey")

Phonic Ear, Inc., 250 Camino Alto, Mill Volley, CA 94941. ("Hondivoice 110," "Handivoice 120," "Vois 130," "Vois 140")

Plantronics, Inc., 350 Dell Ave., Compbell, CA 95008. ("Vu-Phone")

Possum, Inc., 82 8irch Ave., Little Silver, NJ 07739. ("Possum 16," "Possum Cammunicator 100," "Possum Listen & Leorn," "Possum Typewriter System")

Prentke Romich Compony, 8769 Township Rd. 513, Shreve, OH 44676. ("Exponded Keyboord Memowriter," "Express 3," "Autocom," "Veroscan")

Scitronics, Inc., 523 So. Clewell St., P.O. 8ox 5344, Bethlehem, PA 18105. ("Form-A-Phrose")

Sharp Electronics Corp., 9 Sharp Plazo, Poromus, NJ 07652. ("Sharp Memowriter" Models 7001 & 7100)

Sheo Products, Inc., P.O. Box 184, Clowson, MI 48017. ("Speciol Friend")

Specialized Systems, Inc., 11339 Sorrento Volley Rd., Son Diego, CA 92121. ("SSI 100," "SSI 220," "SSI 240")

Telegraphics, P.O. 8ox 1061, Corrolton, TX 75006. ("Scon & Spell")

Telesensory Systems, Inc., 455 N. 8ernardo, Mountoin View, CA 94043. ("Conon Communicator" ond "Mark 2")

Texos Instruments, P.O. 8ox 10508, Lubbock, TX 79408. ("Language Tutor," "Speok 'N Spell," "Vocoid")

Ultrotec, Inc., P.O. 8ox 4062, Madison, WI 53711. ("Superphone")

Words +, Inc., 622 S. Foir Ooks, Sunnyvole, CA 94086. ("Words Plus Living Center")

ZYGO Industries, Inc., 8ox 1008, Portlond, OR 97207. ("ZYGO 16C" ond "ZYGO Model 100")

Endoscopy, A Growing Part of Medicine

Charles M. Mansbach, II, M.D.

GASTROENTEROLOGISTS are dactars who are interested in the diagnasis and treatment af disarders af the esaphagus, stamach, intestinal tract, calan, liver, and pancreas. This subspecialty af internal medicine had few practitianers until beginning in the late 1960s when the widespread use af flexible endascapes began. Since that time, grawth af this subspecialty has been nathing shart af phenamenal mainly due ta the subject matter af this article: endascapy. Ta understand what differences endascapy has made ta the practice af medicine, we first must explore what an endascape is and what it can da.

An endascape is an instrument that literally "sees in." That is, an endascape is any instrument by which a dactar can laak inside any part af the bady. We will take this ta mean any part af the intestinal tract. As we examine the histary af the develapment of this instrument, it will be rapidly understood why there were relatively few practitianers af this art up until the present day.

Dactars first develaped an instrument in the middle part of the 19th century which cauld laok inside the stamach. Dr. Kussmaul, wha invented this instrument, was inspired by a sward swallawer he happened ta see an a Sunday strall. The amaunt af light able ta be generated by the alcahal-turpentine lamps in use at that time, hawever, was not great enaugh ta make this instrument warthwhile. In 1906, electric light bulbs were miniaturized and instruments were develaped that taak advantage af this fact. This culminated in 1932 in the develapment af an instrument that had bath a stiff and a flexible partion. The flexible portion, which was in the stomach, cauld be maved sa that a reasanable partian of the stamach wall cauld be visualized.

In 1958 the first tatally flexible gastroscape was invented. This was the first instrument that did nat require the sward-swallowing technique. What allawed the development af the tatally flexible instrument was the use af fiberaptics. In these fiberoptic instruments, thausands of tiny glass rods are tied tagether into what is termed a fiber bundle. These glass rads are each specially caated sa that they pick up anly a small fractian af the tatal scene that is viewed. All the fiber bundles tagether then allaw the entire scene ta be visualized as a whale. Withaut this special caating, each fiber bundle might see the entire scene and ta the viewer it wauld appear as thausands af miniature views of the same thing. Modern day fiberoptics has enabled the successar instruments to the first flexible gastroscape ta have excellent optical quality. Subsequent ta the develapment af flexible endascapes far examinatian af the upper intestinal tract, instruments based on the same principles were develaped for study af the calan.

The endascapes that we will discuss have twa general purpases. The first functian is diagnasis, which we will explare first, and the secand is treatment, which is becaming a factor of greater and greater impartance in endascopic usage.

Diagnosis

Esophagogastro-duodenoscopy: What da dactars see when they laok inta the intestinal tract and why da they wish to do it? In terms of upper intestinal disease, the doctor perfarming the endoscopy (the endoscapist) is able to examine the esophagus, the stomach, and the first portion of the small intestine called the duodenum. These areas are the site of large numbers af patient camplaints including peptic ulcer disease, heartburn, and intestinal bleeding. Using the endascope the dactor can evaluate the extent and severity of esaphagitis (inflammation of the esophagus) which usually results fram the reflux of gastric acid up inta the esaphagus. Camplaints of faad sticking in the esaphagus after being swallawed are rautinely investigated by endascapy ta rule out the presence af an esophageal tumar or stricturing af the esaphagus (narrowing af its inner diameter) resulting from the canstant reflux of gastric acid. Endascapy is alsa useful in seeing whether or nat the patient has enlarged veins in the esaphagus due ta severe liver disease.

In the stamach and first partians af the duodenum, dactars are usually laaking far the presence of ulcers. If an ulcer is faund in the stamach, the questian af its cancerous nature is always raised. Ta rule aut cancer, the ulcer can be biapsied directly through the endascape and specimens can be abtained far cytalagic examinatian. Ulcers usually appear as a yellow area in the narmally pink-red backgraund af the gastric surface, ar mucasa. Sametimes the ulcer beds are filled with debris; sametimes, especially after bleeding, clats ar black scabs appear at the surface af the ulcer.

At ather times, no ulcer is seen but, rather, erosians of the stomach lining or a generalized inflammatory response called gastritis. Gastritis usually appears as inflammatian daes elsewhere as reddened raw-appearing mucosa. These types of lesions are often caused by alcohol or drugs such as aspirin.

Occasionally polyps of the stomach are found. They are biopsied and

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cytologic specimens are obtained to rule out as well as possible their cancerous nature. Ofttimes, they may be safely removed through the endoscope as will be discussed later.

Patients who have had previous gastric surgery, especially those in whom part of the intestine has been brought up to an opening made in the stomach, often complain of either pain or bleeding. In this instance, the endoscope is an invaluable tool to examine for the presence of an ulcer in the opening between stomach and intestine made by the operation. Sometimes patients complain of vomiting although the vomited food has never left the stomach. In such cases, doctors wish to examine the valve, called the pylorus, which is between the stomach and the first part of the duodenum, where narrowing may occur due to longstanding peptic ulcer disease or where a tumor might have obstructed the outflow of gastric contents.

Endoscopic retrograde choledocopancreatography: A different type of endoscope is used for evaluating the common bile duct and pancreatic duct. These ducts are the channels whereby bile and pancreatic juice, respectively, gain access to the intestine. In this case, the endoscope that is used has its viewing port on the side rather than in front and is equipped with a special channel which allows the introduction of a long catheter. When the endoscope is placed opposite the mound-like opening of the common bile and pancreatic ducts in the first portion of the small intestine, a catheter is advanced into these small ducts. X-ray-visible dye is injected through the catheter, first into the pancreatic and subsequently into the common bile duct. By looking at the image of the ducts on x-ray, doctors can pick out stones in either the pancreatic or biliary ducts, patterns suggestive of tumors involving these organs, or other diseases such as chronic pancreatitis and cysts of the pancreas.

Colonoscopy: Colonoscopy is the examination of the colon by the use of a similar instrument. In order to examine the colon the patient is given a special salt solution which causes evacuation of all fecal material from the colon. The colonoscope is then inserted into the rectum and the colon is examined to the cecum where the colon proper begins. In some cases, the last portion of the small intestine may be entered via the cecum. In examining the colon, doctors are mainly concerned with the presence or absence of colonic cancer or polyps. Other reasons for doing colonoscopy include investigation for intestinal bleeding or evaluation of the extent of inflammatory bowel disease such as ulcerative colitis or Crohn's disease of the colon.

Treatment

Endoscopy is entering a new phase in which treatment is provided in selected cases after a diagnosis is made. Each modality of treatment will be considered separately.

Sclerotherapy: Sclerotherapy is used to prevent rebleeding from enlarged veins (varices) in the distal esophagus in patients who have been shown to bleed from these vessels. Large amounts of blood are often lost when bleeding occurs in this situation. These enlarged veins usually arise in patients who have cirrhosis of the liver and they form an escape route for blood that is unable to pass through the liver. The physician uses an endoscope to visualize the varix and injects it with the sclerosing agent which obliterates the vein. This is repeated until two to three veins have been injected. The patient is then brought back weekly for repeated injections until all veins have been successfully injected and no varices are visible.

Polypectomy: Polypectomy or removal of polyps is usually performed via the colonoscope because most polyps of the intestinal tract are found in the colon. The doctor inserts the colonoscope to the level of the polyp. A snare wire is inserted through the colonoscope and it encircles the base of the polyp. An electrocautery-coagulation current is passed through the wire which separates the stalk of the polyp from the colonic wall. The polyp is then retrieved for pathologic examination. Multiple polyps can be removed in this fashion at one time. These are important procedures because removal of the polyps lessens the likelihood of colonic cancer. Polyps of the stomach can also be removed in a similar fashion.

The advantage of this type of procedure is that patients who used to require a surgical operation for polyp removal can now have this performed essentially as an outpatient procedure or one that requires only a one-night stay in the hospital.

Sphincterotomy: After gallbladder removal, stones are occasionally found in the biliary system. These stones may give rise to major symptoms and therefore must be removed. In the past, this has required a surgical procedure with an exploration of the common bile duct. Usually a T-tube (a tube shaped as a T) would be placed in the duct and bile would drain through the tube to the outside for several weeks after the procedure. With sphincterotomy, however, no operation is required and usually no tubes are left in the duct after the procedure. To perform the procedure, doctors visualize the sphincter or the outlet of the common bile duct and pancreatic duct into the duodenum. The sphincter, which normally has a small opening, is then cut to a precise degree which enlarges the opening for both bile and pancreatic juice to flow into the small intestine. The opening is made large enough (usually 1.2-1.5 cm) so that stones may be extracted from the duct using another catheter which has a balloon on it. The catheter is passed so that the balloon is inflated behind the stone and the stone is then retrieved from the duct by pulling the balloon out through the newly enlarged sphincter. This procedure may also be performed on those patients who are debilitated or who are quite aged if they have symptomatic stones in the

camman bile duct even if their gallbladder is present. In this case, it is haped that an aperatian ta remave the gallbladder wauld nat be required.

Laser Therapy: Gastraenteralagists have explared ways ta use lasers in the treatment of gastraintestinal disarders. Far gastraenteralagists, lasers are a means of administering heat ta a precise area af the lining of the intestinal tract. Different types of lasers have different usages depending upan haw deep the heat must penetrate inta the tissue. The laser most cammanly used by endoscapists is the Ng:YAG which gives off a greenish calared light. Light guide wires have been develaped that can be inserted thraugh the endascape and reach the area ta be treated. When the laser is turned on, the area af the intestinal tract that is being lased undergaes a sequence af reactians, the end result af which is char or vaparizatian. Care must be taken so that a thraugh-and-thraugh burn af the intestinal tract is not praduced. This can be dane using carefully calibrated machinery far standardized amaunts af time. As laser therapy progresses, the endascapist watches the results thraugh the endascape. His best guide is ta fallaw the knawn sequence af events that accurs under laser therapy and ta stap when he feels that enaugh treatment has been given.

Anather use far laser therapy is ta coagulate small arteries just belaw the surface of either the calan ar the stamach. These appear as a tangled web af vessels ar as a bright red dat accasianally with single branches emanating fram the central facus. These sa-called telangiectasias may bleed silently, especially in alder peaple. Laser therapy can be applied ta these vessels and adequate coagulatian accamplished sa that bleeding daes not recur fram that site. Using a different type af instrument, electracautery units can accomplish the same thing and stap bleeding.

An additional palliative therapeutic use af the laser is the abliteratian af the partian af a cancer abstructing the esaphagus. In this situation, the abstructing tumar is progressively vaparized by the laser heat until there is na abstructing tumar left within the lumen of the esophagus. An Argan laser is afttimes used for this type af work.

Relief of Impacted Food Substances: Occasianally faad, usually a piece af meat that has been paarly chewed, gets stuck in the lower portion af the esaphagus, almast always in assaciatian with narrawing af the esophagus. This situation produces an intensely uncamfartable sensatian in which further faad ar fluid cannot be swallawed without vamiting. The physician passes the endascape ta the site af abstructian and the faad causing the problem is visualized. The preferred method is ta attempt ta push the food into the stamach which is done while laaking ta be certain that the opening in the esophagus is large enaugh to permit passage af the endascope and the impacted faad. Alternatively, the food can be picked apart piecemeal by small farceps. Occasianally, it is necessary to extract the impacted faad by gripping it with a forceps and remaving the endoscope with the farceps and the faad.

Endoscapy has grawn from a simple adjunct ta the diagnasis af gastraintestinal diseases to a powerful therapeutic taal. Undaubtedly, as the years progress, more and more uses will be devised far it. At present it remains an extremely useful taal in the armamentarium af physicians. Diagnases which heretafare had been anly educated guesses can now be shawn ta be accurate ar false. Treatment can be administered in a wide variety af areas, aften avaiding the need far a formal surgical procedure. Far these reasans, endoscopy is playing a majar rale in the practice of medicine and will undaubtedly play an even greater role in the future.

Acne and Accutane

Claude S. Burton, M.D., Russell W. Eyre, M.D., and J. Lamar Callaway, M.D.

Sacially crippled, casmetically disfigured, and financially exhausted in search af a cure, acne sufferers take heart. Our recent experience with Accutane (a recently released aral treatment far acne) suggests the ance familiar "ice-pick" scarring af acne is naw an endangered species. Accutane, a synthetic form af the naturally occurring vitamin A bypraduct Isatretinain was first marketed far acne in the U.S. in September 1982. Accutane praduces a permanent remissian af acne in the vast majority af patients fallawing a single 16-20 week caurse af therapy. Therapy costs less than we anticipated in aur article in this *Jaurnal* in May 1983, yet remains a burden far many. Tablets ta complete the recammended 16-20 week caurse af therapy cast $200-$400. The necessary doctar visits and lab studies add an additianal $150 ta the cast. Still, Accutane is a bargain if one cansiders the lang-term cost of alternative, less effective therapies.

The price one pays far marvelaus results includes many uncamfartable side effects. Accutane is a patent inhibitar of oil production essential for lubrication of the skin and mucous membranes. Everyone experiences chapped lips that may crack and bleed. Dry eyes may produce conjunctivitis and vaginal dryness may interfere with sexual intercourse. Dry nasal mucous membranes may lead to nosebleeds. If the skin dries to the point of cracking, itching and rash may appear. We ask all patients to use lip moisturizers from the start of therapy. Artificial tears and moisturizers for skin and mucous membranes are recommended as necessary. Fartunately, since Accutane is nat stared in the bady, these side effects vanish when therapy ceases.

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The ideal therapeutic dase is clase ta the taxic dase. Therapy must be individualized. Adjustments are often necessary during a 16-20 week caurse. In additian ta the drying effects, there are ather side effects taa numeraus ta list. Thinning af the hair, increased sun sensitivity, musculaskeletal aches and pains, irregular waund healing, and fatigue are nated frequently. These are rarely seriaus, resalve spantaneausly after cessatian af therapy, and respand ta symptamatic treatment. Twa mare seriaus assaciatians are bowel inflammatian and cataract farmatian nated in a few patients. As with any drug, patients are advised to stap therapy and cansult their physician if unusual symptoms appear. Long-term therapy is mare hazardaus, praduces permanent bony and acular changes, and is nat indicated far acne. If a secand course must be given, a haliday between caurses is advisable. Frequently patients continue to note improvement long after stapping the drug.

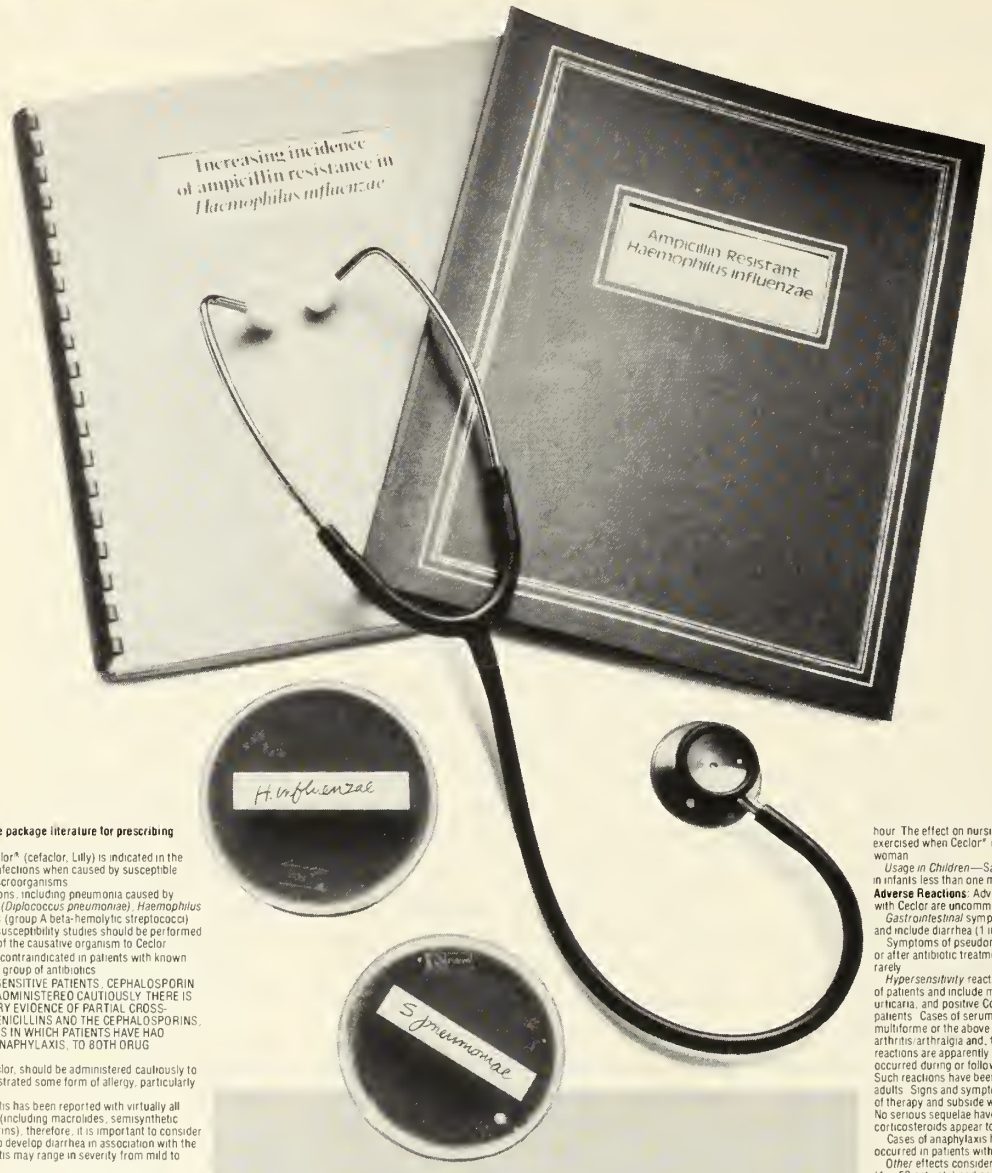
Oil production returns, acne does nat. What other actions of this drug are responsible far the sustained improvement? Accutane has potent, enigmatic influences on cellular development. Malignant nerve cells harvested from cancer patients transform to normal cells if grown in the presence of this drug. Trials in cancer patients are in progress. Such observatians suggest a developmental role for Accutane in the skin of acne sufferers. For instance, a change in cells at the neck of oil glands would prevent blocked oil glands — the earliest lesian in acne. Experience has shawn that lower dases af Accutane will inhibit ail praduction and clear acne tempararily. Higher dases are assaciated with sustained impravement in spite af the return af oil praductian. Thearetically, the higher dases induce permanent changes in the skin af acne sufferers.

It is the patent influence an develaping cells that scares us the most. Any waman who becomes pregnant while taking the drug ar is pregnant when therapy is started will likely praduce a defarmed child. Few agents are as paisanaus ta the develaping fetus. Extreme cautian ta avaid the use af Accutane during the period of canceptian ar gestation is indicated. Despite these warnings, numeraus harribly defarmed children have been praduced. On the other hand, ance therapy is complete, childbearing is safe. Accutane is rapidly eliminated fram the bady. The manufacturer recammends waiting ane menstrual cycle after therapy before attempting canceptian.

Far same, the therapy has arrived too late. The fire department can quench a burning roof with water but all the water in the world will not reshingle the roof. The same is true in acne. This drug will arrest the process but do nothing for the scarring already present. Our goal is to treat patients before permanent damage has been done. We finally have an agent that produces consistently marvelous and permanent results.

We wish to emphasize again that this therapy for a common disease requires the close supervision of a doctor. You are at great risk if you acquire a quantity of Accutane and treat yourself. Don't do it!

An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor
Pulvules®, 250 and 500 mg

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor® (cefaclor, Lilly) is administered to a nursing woman

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information

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Drug Therapy of Systemic Fungal Infections, Part I

Mark Gross, Pharm.D.

As antibiotic and antineoplastic therapies have become more potent, serious fungal infections have increased in incidence.[1] Although newer antibiotics more effectively eliminate competitive forces, fungi may proliferate unchecked, resulting in disseminated infections. Multisystem mycoses are infrequent in the normal host and the pathogen is usually contained at the site of entry. In hosts with immune function altered by other drugs (e.g., corticosteroids, cancer chemotherapy) or diseases (e.g., AIDS, congenital immunodeficiencies) and who may be receiving numerous antibacterials, systemic fungal infections often lead to morbid or fatal outcomes. Common fungal infections include candidiasis, blastomycosis, histoplasmosis, coccidioidomycosis, and cryptococcosis. Treatment is further complicated by the tendency of more potent antifungals to demonstrate increasingly severe side effects. Effective antimycotic therapy may therefore be limited by iatrogenic complications.

This review is intended to discuss the more widely used antifungals with respect to their clinical indications, pharmacology, toxicities, and pharmacokinetics.

Ketoconazole (Nizoral)

Ketoconazole, an imidazole derivative, exerts its antifungal effects by disrupting ergosterol synthesis and thereby inhibiting growth of the cell membrane.[2] The imidazoles are generally considered fungistatic compounds, but at higher concentrations cidal actions involving RNA have been observed.[3, 4] Ketoconazole is FDA-approved for the treatment of candidiasis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, blastomycosis, and chromomycosis. The drug's major advantage over amphotericin B is that it can be used orally and that it is less toxic.[11] Unfortunately, many clinical studies of ketoconazole have involved non-controlled groups or case reports, making an evaluation of its clinical efficacy difficult at the present time.

Dismukes et al, in a non-controlled, non-randomized study, treated 52 patients with 100-600 mg/day of ketoconazole for blastomycosis, non-meningeal coccidioidomycosis, sporotrichosis, histoplasmosis and cryptococcosis.[5] Doses were increased according to the severity of the infection, and treatment lasted from 13 days to 12 months. Overall, 52% of patients were judged cured or improved while 48% either relapsed, failed to improve, or died of other complications. Those with histoplasmosis showed a superior response followed by those with non-meningeal coccidioidomycosis, cryptococcosis, sporotrichosis, and finally blastomycosis. Varying the daily dose could not be correlated with outcome but prolonged therapy greater than six months did prove beneficial. Although positive effects were demonstrated, this study has been criticized for the relatively short and variable duration of treatment, failure to include controls, and poor criteria for clinical cure.[6] Before a mycosis can be assumed cured, a patient should be monitored for as long as two years for histoplasmosis and cryptococcosis and five years for coccidioidomycosis.[6] It has also been suggested that a greater therapeutic outcome could be achieved if ketoconazole were administered following amphotericin B induced remission.[6]

A preliminary study suggests that high doses of ketoconazole may effectively control CNS infections of coccidioidomycosis or histoplasmosis.[7] Six patients, four of whom received concurrent amphotericin B, also took high doses of ketoconazole (600-1200 mg/day) for indefinite periods. Two patients ceased amphotericin B therapy while showing improving symptoms or no clinical disease. Although ketoconazole penetration into the CNS is minimal (1-5% of serum levels), the data demonstrate that this regimen may have a therapeutic effect.[7] Unfortunately the fungistatic nature of the drug will probably necessitate life-long continuation to assure suppression of the disease. However, when compared with the possible complications of amphotericin B, this may be an acceptable alternative.

Ketoconazole is the drug of choice for chronic mucocutaneous candidiasis.[3] Peterson et al, using 100-600 mg/day of ketoconazole, documented favorable responses in six of six patients and later in five of six from a previously placebo-controlled group.[8] Treatment lasted for at least six months in all patients. Mucosal improvement was often noticed before cutaneous improvement.

Peak plasma levels of ketoconazole occur 2-4 hours after oral dosing with a maximum of 1.6-6.9 mcg/ml in the serum after a 200 mg dose.[9] Normal doses begin at 200 mg once daily and may be increased up to 600 mg/day. Better GI absorption occurs in the presence of food and acid.[10] Absorption is reduced when the drug is consumed with antacids, cimetidine, or ranitidine.[10] The drug is highly protein-bound and only negligible amounts penetrate the CSF.[11] Ketoconazole is primarily excreted as an inactive metabolite in the feces and less than 5% of the drug is excreted unchanged in the urine.[12] Renal failure would not be expected to result in delayed elimination or toxicity and it is not yet clear whether liver disease would also affect ketoconazole elimination. Case reports of patients receiving ketoconazole with moderately severe liver function

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were not associated with drug accumulation.[13]

The most serious toxic reaction to ketoconazole is hepatotoxicity which may occur in up to 5% of patients and results in elevated SGOT levels.[3] Such toxicity, however, does not appear to be dose-related.[3] It is recommended that the drug should be discontinued if any signs of symptomatic liver disease occur and liver function should be checked periodically.[3] Ketoconazole may cause a dose-related depression of serum cortisol and testosterone levels, although the clinical significance of these changes is minimal.[3] Other side effects include nausea and vomiting (3%), abdominal pain (1.3%), pruritis (1.7%), headache (0.9%), and gynecomastia (3-8%).[11]

Presently, no conclusions relative to ketoconazole's effectiveness in systemic mycoses can be made due to the paucity of large, controlled, randomized trials. It is apparent, however, that the drug may effectively suppress a number of serious mycoses such as mucocutaneous candidiasis, histoplasmosis, and coccidioidomycosis. The drug may be especially useful as a suppressive agent following fungicidal therapy with amphotericin B in susceptible infections, but this regimen has not been tested. Long durations of treatment often greater than 6 months will be necessary in most infections due to the fungistatic nature of the drug. In candidiasis, the effectiveness of ketoconazole remains to be determined but it may have potential benefit for this increasingly common infection.

Amphotericin B (Fungizone)

Amphotericin B is currently the most effective antifungal agent available yet also the most toxic. Despite its severe side effects, it is the standard by which other systemic antifungals are compared. The mixed hydrophobic and hydrophilic properties of ths fungicidal drug allow it to bind to fungal (or protozoal) ergosterol, the fungal equivalent of cholesterol, disrupting membrane integrity and intracellular electrolyte balances.[3] Besides its direct antifungal effects, amphotericin B may also augment the host's immunologic mechanisms.[43]

Amphotericin B is often used in the treatment of candidal infections in immunocompromised or post-surgical patients. Low doses of amphotericin B may be effective in some of these infections, thus avoiding the nephrotoxicity common to higher doses. Medoff et al. treated fourteen patients with candidal pneumonia, fungemia, urinary tract infections, esophagitis, and vaginitis using total doses that ranged from 12 to 355 mg over four to ten days.[15] Infections were eradicated in 12 patients and the authors often noted improvement after one dose. Excluded were patients with candidal meningitis or endocarditis because these diseases require higher doses and prolonged treatment. However, no prospective study has defined the appropriate dose or duration for disseminated candidiasis, particularly in the neutropenic patient, where longer courses of therapy may be needed.

Cryptococcal meningitis is associated with a high failure rate of treatment, especially in immunosuppressed patients. Bennett et al. compared the effectiveness of a ten week course of amphotericin B alone with a six week course of amphotericin B and flucytosine in 51 patients with cryptococcal meningitis.[16] Although the study was designed only to determine whether the combination was equivalent to amphotericin B alone, the authors concluded that the combination was superior to amphotericin B alone because of the shorter treatment interval, more rapid CNS sterilization, and fewer deaths in patients receiving both drugs. However, flucytosine has its own potential toxicity and, in fact, with either regimen only approximately two-thirds of patients were successfully treated. A recent case report successfully used equivalent doses of amphotericin B and flucytosine to treat a 47-year-old man with a candidal lung abscess, eradicating the abscess after 26 days of combination therapy.[17] The authors suggest that this combination is synergistic against candida, but there is no evidence that the infection would not have been eradicated as rapidly using amphotericin B alone. Furthermore, there are no prospective studies to suggest that the combination would be more effective than single agents for yeast (i.e., candida) infections.

Fungal resistance to amphotericin B has not been frequently documented although it may occur in cases where high doses of the drug have failed to achieve a cure. Pappagianis et al documented acquired amphotericin B resistance in a rare form of candida *(C. lusitaniae)* that demonstrated MICs of 0.31 mcg/ml before amphotericin B treatment and 30 mcg/ml following amphotericin in a single case of fatal candidemia in a leukemic male.[18] It is presently conceded that *in vitro* resistance to amphotericin B is not clinically important. However, widespread use of amphotericin B in severely immunocompromised hosts may lead to production of virulent mutants and surveillance must therefore continue.

Rifampin, an antibacterial that inhibits RNA synthesis, has been studied for possible antifungal synergy with amphotericin B *in vitro* and in animals with mixed results. Medoff found rifampin to be synergistic *in vitro* with amphotericin B against strains of *Histoplasma, Saccharomyces,* and *Aspergillus* and the combination appeared to prolong survival and decrease morbidity in mice.[19] However Ernst et al failed to duplicate this trend in experimental candidal infections in corticosteroid-treated guinea pigs.[20] Presently there is no definitive evidence indicating that rifampin and amphotericin B should be used together in a clinical setting.

The distribution of amphotericin B follows a three-compartment model with a volume of distribution of 5 L/kg.[21] More than 90% of the drug is protein bound and thus poorly dialyzable.[22] Less than 5% of the drug is absorbed after oral administration.[3] Peak serum levels approximate 2 mcg/ml with a distribution half-life of 24-48 hr and an excretion half-life of 10-12 days.[21] A single intravenous dose may provide therapeutic concentrations in the bile, urine, or stool for up to one week.[3] Although renal failure may not affect amphotericin B levels, it may predispose the kidneys to nephrotoxicity.[23]

The major route of elimination still remains unclear. Craven et al found that the bile and urine may account for 40% of eliminated amphotericin B. Detectable levels of the drug have been found in kidney tissue of a patient 12 months after a 21 gram cumulative dose was completed.[25] Therefore a large percentage of the drug may undergo

either long term tissue sequestration or elimination via an as yet undetermined metabolic pathway.

Because of the variation in pathology, fungal susceptibility, and patient sensitivity, the dose of amphotericin B may vary from patient to patient. The most serious mycoses will require a daily dose of 0.3-1.0 mg/kg, while those with less severe infections may be adequately treated with doses as small as 15 mg/d. Initially a test dose of 1 mg over 2 hr should be given while the patient is observed for an anaphylactic reaction. Ten additional milligrams may be administered if no reaction develops, but if the patient is acutely ill with infections such as disseminated aspergillosis as high as 0.3-0.5 mg/kg may be given. The dose may be increased by increments of 5-10 mg per day until a full daily dose has been achieved. Patients who are intolerant to daily doses may receive the drug on alternate days without compromising the antifungal effect.[26] The risk of nephrotoxicity, however, is not reduced with alternate-day treatment.[26]

Intrathecal administration of amphotericin B usually begins with 0.1 mg, increasing in 0.1 mg intervals to 0.5 mg per week.[26] Unfortunately this procedure is fraught with risks such as subarachnoid hemorrhage, severe intractable headaches, and seizures and should only be undertaken as a last resort.

The most widely recognized toxic manifestation of this drug is nephrotoxicity, and may be due to a number of mechanisms. This occurs by drug-induced decreases in glomerular filtration rate, renal tubular acidosis, decreased serum potassium and hypomagnesemia.[27] Concurrent administration of aminoglycosides may hasten renal toxicity.[28] A recent report suggests that patients may be predisposed to this nephrotoxicity if they are sodium depleted secondary to diuretics, low sodium diets, anorexia, or vomiting.[29] In five patients sodium loading was associated with improved renal function which permitted amphotericin B therapy to be continued to the completion of antifungal therapy. It is not known whether these findings imply that a high salt intake before treatment will prevent nephrotoxicity.

Other toxic reactions include normocytic, normochromic anemia, which may occur due to a reduction in erythropoiesis, and after several weeks of amphotericin B, hematocrit levels are expected to be in the 25-30% range.[30] Thrombocytopenia associated with amphotericin B has been reported in a leukemic male; it resolved when the drug was discontinued and recurred upon rechallenge. To minimize thrombophlebitis, amphotericin B infusions are prepared with a phosphate buffer to raise the pH above 6.5. Hydrocortisone (20-50 mg per liter) and heparin (1 unit/ml) also may minimize irritation. To prevent fevers and chills during administration, the patient may be premedicated with diphenhydramine 25-50 mg, acetaminophen 300-600 mg, or meperidine 25-75 mg. The drug must be prepared in saline-free solutions in order to avoid inactivation. Generally the drug is given over 6-8 hours. Some patients may tolerate faster infusions, although there is much individual variability.

Part II will appear in the September 1984 issue of the NCMJ.

References available from the NCMJ editorial office.



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EDITORIAL

A View from the National Academy of Sciences: Science and Creationism

Frank Press

THE National Academy of Sciences with the support of a North Carolina foundation (Mary Reynolds Babcock) has published an excellent paper which should be in the hands of all the members of school boards and school committees. It should be made widely available to all non-science teachers who may need accurate information about evolution.

I quote the Preface by Frank Press in its entirety. Press is the president of the National Academy of Sciences.

"Before you begin to read this discussion of science and creationism, please take a careful look at the front and back covers of this booklet. The front cover depicts the world as we know it to be today. The back cover illustrates the world as people believed it to be in the days before Columbus sailed to the New World. Both views have a place in our lives — but one belongs in the world as we have come to know it and one belongs in history. Both views, by the way, are the products of science. How then can the two views be so different? The answer lies at the very heart of the nature of this system of study we call 'science.'

"In science, everything we observe, measure, or discover must be successfully tested again and again before it is accepted as valid and as factual evidence of what is real. During the application of this scientific method, scientists review their data carefully — and with a healthy skepticism. Most important, the scientific method requires that the fact-seekers remain open-minded, are willing to accept changes indicated by the signposts of evidence. It is easy to see how this approach encourages the acceptance of change, which in turn fosters original thought, new ideas, and new hypotheses, all converging on a better understanding of nature.

"One might think of Columbus's voyage to the New World as a test of the hypothesis that India, which lay to the east, could be reached by sailing westward on a round world. As a result of his exploration and many subsequent observations, including those from voyages into space, we now know that our world actually looks as it is shown on the front cover of this booklet.

"And that is why scientists, such as those of the Council of the National Academy of Sciences who asked that this booklet be prepared, feel that teaching the scientific theory of evolution alongside creationism is inappropriate. Teaching creationism is like asking our children to believe on faith, without recourse to time-tested evidence, that the dimensions of the world are the same as those depicted in maps drawn in the days before Columbus set sail with his three small ships, when we *know* from factual observations that they are really quite different.

"It is false, however, to think that the theory of evolution represents an irreconcilable conflict between religion and science. A great many religious leaders and scientists accept evolution on scientific grounds without relinquishing their belief in religious principles. As stated in a resolution by the Council of the National Academy of Sciences in 1981, however, 'Religion and science are separate and mutually exclusive realms of human thought whose presentation in the same context leads to misunderstanding of both scientific theory and religious belief.'

"The theory of evolution has successfully withstood the tests of science many, many times. Thousands of geologists, paleontologists, biologists, chemists, and physicists have gathered evidence in support of evolution as a fundamental process of nature. Our understanding of evolution has been refined over the years, and indeed its details are still undergoing testing and evaluation. For example, some scientists currently debate competing ideas about the rate at which evolution occurred. One group believes that evolution proceeded in small, progressive stages evenly spread throughout the billions of years of geological time; another group believes that there were alternating periods of relatively rapid and slow changes throughout time.

"Creationists sometimes cite this debate as evidence for disagreement about evolution among scientists; some even suggest that scientists who advocate the latter hypothesis are actually supporting a process similar to that of creationism. What these creationists fail to understand, however, is that neither scientific school of evolutionary thought questions the scientific evidence that evolution took place over billions of years. Rather, the debate centers on only the finer details of *how* it took place.

"Debate among scientists is expected. And the products of such debate over the years have been truly astonishing. Scientific debate influenced the planning of Columbus's voyage and, more recently, the explorations of space. But debate does not mean resurrecting old theories that have long been invalidated by observations and experiments. Theories that are supported by evidence, and which survive the rigorous testing of the scientific method, are passed on to future generations. Examples are the germ theory of disease; the theory of gravity, which controls the movement of planets; and the theory of evolution. Those that are discounted by the evidence, and which fail by the scientific method, are of interest only to the historians of science.

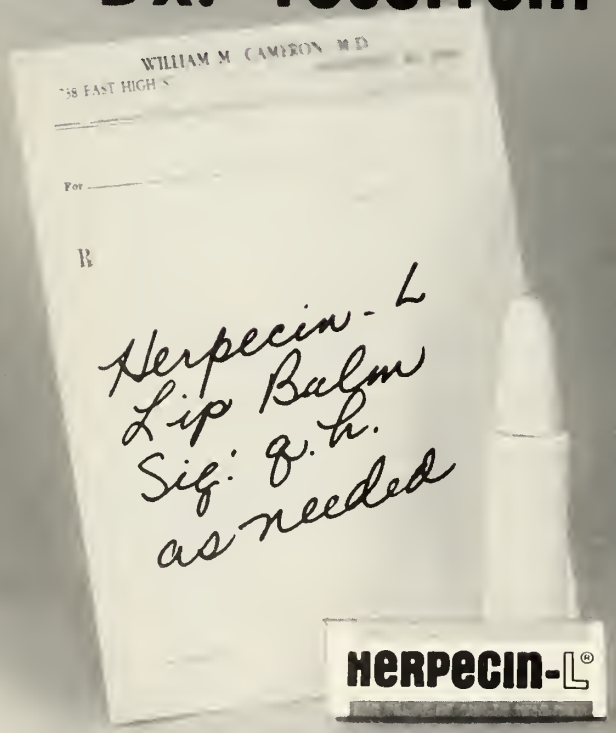
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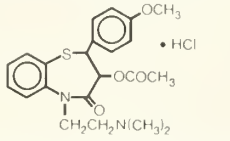
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CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis- The chemical structure is:



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CLINICAL PHARMACDLDGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIDNS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia

The following additional experiences have been noted.

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

DVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** – CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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Termination Without Extreme Prejudice — Amanita Phalloides

Ronald B. Mack, M.D.

I must admit she was beautiful; when she first came into view I was immediately struck by her lovely figure. Her stems were almost perfect. She was dressed perfectly for the warm weather, and a faint fragrance seemed to surround her. I impulsively wanted to grab this vision of loveliness and take her to dinner but I just could not; she was not alone nor was I. Besides, although she looked like an angel there is no question that she was wild, and people have since remarked that she has the reputation of being a killer. I was able to get her name — Amanita Phalloides (melodious, is it not? Probably foreign) but not her phone number or astrological sign. She was so gorgeous that you wanted to take a bite out of her.

Alright, I was only fooling — Amanita Phalloides is certainly extremely seductive and dangerous, but not as a person, for you see it is merely the name of one of the most toxic wild mushrooms in the world. It seems that there has been an increase in serious cases of mushroom poisonings in the U.S. in the recent past. There is probably no one reason for this increase but it is well known that many people love to search for and eat wild mushrooms. What is a mushroom after all? Mushrooms belong to a very large group of simple plants known as fungi; they possess no seeds, roots, flowers, chlorophyll or leaves. The mushroom is merely the fruiting part of the plant that is visible above ground — apparently most of the plant (a network of tiny threads) is hidden. (Think of this the next time you eat some.) There are probably 5000 species of mushrooms growing wild in the United States and 50-100 species are toxic. The Amanita Phalloides is only one of many toxic mushrooms but it is extremely poisonous and is thought to be responsible for the majority of fatal mushroom poisonings in Europe. It has only been positively identified as growing wild in our country since the 1970s.

Many people refer to these poisonous mushrooms as toadstools (don't let the name fool you, it does not mean frog doo-doo) which is derived from the Teutonic word for death. There are many very good references explaining the division of toxic mushrooms into groups but this paper will attempt to discuss the most toxic division, i.e., the *cyclopeptides* of which Amanita Phalloides is a prominent member. The toxins in this cyclopeptide group are unusually virulent and are believed to cause 95% of fatalities secondary to mushroom poisonings. The scariest genus in the cyclopeptide group is the Amanitas as has been mentioned, but why? These mushrooms contain thermostable toxins which are known as *amatoxins*. The amatoxins, especially one known as *amanitin*, destroy cells by inhibition of nuclear RNA polymerase II (now that sounds serious!!) and therefore interfere with both RNA and DNA transcription. The cells die and do not reproduce, especially those that are hit by the initial contact with the toxin and those with the most rapid rates of turnover, e.g. hepatocytes, renal tubular cells and GI tract mucosa cells.

To be perfectly frank, I find clinical toxicology very exciting (but then again I think Indira Gandhi is a real fox!!). To continue to be perfectly frank, inquiries from house staff or medical colleagues concerning mushroom ingestions can cause me to almost become anaphylactoid. They are not terribly easy cases for most of us to manage, let alone to pontificate upon. One of the better ways to approach this problem is to function according to the following general principle: the time of onset of symptoms following ingestion of a poisonous mushroom parallels rather closely the severity of the toxic encounter. There are exceptions of course, but the less severe, more-or-less self-limiting mushroom toxins cause abnormal clinical features within 15 to 120 minutes following ingestion. The really potent mushroom toxins, the ones that can kill, do not cause symptoms until 6 to 18 hours post ingestion. According to a recent book: "Exceptions always outnumber rules and there are always exceptions to established exceptions and by the time one masters the exceptions, no one recalls the rule."[1]

The Amanita mushrooms causing toxicity are of the long incubation type and this causes great consternation for the health care professional (the patient does not fare too well either) because it gives a false sense of security. To put it another way, mushrooms causing symptoms that are delayed for 6 to 24 hours after eating them are the ones that can kill the patient and it behooves you to try to diagnose these cases and stave off death if you can. The mortality rate is quite high indeed. The long latent period seen with Amanita ingestions may be due to the period of time necessary for the absorption of the toxin into the cells of the GI tract and the inhibition of RNA transcription to take place.

The clinical features of amanitin poisoning rather typically appear about 12 ± 2 hr after eating the poisonous fungus and classically is divided into three stages. In *Stage I* there are very severe abdominal cramps, nausea, vomiting and remarkably profuse watery diarrhea (which is best described as "Cholera-like"). This severe gastrointestinal

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

insult can easily last 24-36 hours. Needless to say, the fluid and electrolyte loss can be formidable, leading at times to circulatory collapse. *Stage II* (AKA the latent stage) is present during the next 24 to 36 hours. In this phase there is often a remission in symptoms, especially if fluid and electrolyte replacement has been adequate; the patient appears to be recovering. It is in this stage, however, that laboratory values often look worse than the patient as liver enzymes rise, presaging severe hepatocellular damage and rising BUN and creatinine values allow you to note that renal damage is ensuing. *Stage III* (AKA the final stage and for many it unfortunately is) is the time where many of us feel like calling the patient's religious advisor. In this stage there is massive hepatic necrosis and icterus and acute renal failure as well as encephalopathy, coma, seizures, hypoglycemia, Stage VI bad breath, falling arches, hemorrhoids, etc. and as a health care provider you think you are witnessing the "One Horse Shay" phenomenon. (Remember this poem by Oliver Wendell Holmes where the author describes the breakdown of a carriage that seemed to fall apart all in one day.) Death is due to hepatic and renal failure and to secondary effects on the CNS and the cardiovascular system and usually occurs 4-7 days after eating the mushroom.

How do you go about diagnosing and treating such an awesome enemy as this? Certainly you should at least consider toxic mushroom ingestion in any case of more than simple acute gastroenteritis. Mushroom poisoning is more prevalent in the spring and fall as the moderate temperatures and wet conditions foster fungus growth. Do not forget that the later stages of amanitin poisoning resemble Reye's Syndrome or severe acetaminophen poisoning. If the truth were known there are several conditions that can simulate this poisoning clinically, e.g., poisoning due to carbon tetrachloride or ferrous sulfate or phenylbutazone to name a few. In a perfect world you would make every effort to identify the mushroom you believe is making your patient sick. But this is an imperfect world and not many of us are mushroom experts. You are very fortunate if your area has an experienced mycologist available; ask the college or high school botany teachers if they can help you or the local plant store manager who is often a good source for plant ingestions in general.

The treatment of amatoxin poisoning is mainly supportive with careful attention being paid to the restoration of fluids and clotting factors and the minimizing (if possible) of the renal and/or hepatic failure. Many other treatments have been tried but most are anecdotal and there are no good controlled studies to prove or disprove their efficacy. This is a difficult poison to obtain good data about; how do you measure how much toxin the patient ingested? Apparently most of the amatoxin is excreted within six hours of ingestion whereas many patients seek treatment later than six hours. The treatments that have been suggested include repeated doses of activated charcoal, the use of steroids, cytochrome c, penicillin, thioctic acid and extracorporeal removal of the toxin. Others such as emulsed rabbit brains or horse serum antitoxins are not even considered reasonable choices these days but were at one time. The only therapy that experts seem to agree on is careful monitoring of the patient and replacement therapy as indicated.

I would be remiss if I left the subject of Amanita Phalloides intoxication without mentioning the use of the controversial "antagonist" *thioctic acid*. This product, AKA alpha lipoic acid, is a Krebs cycle coenzyme which is thought to ameliorate hepatocellular damage. Thioctic acid has advocates who believe it is extremely helpful in preventing death in Amanita Phalloides poison cases (as well as other Amanita species), and it has detractors who do not believe it works at all. It is considered a reasonably safe product and the only side effect so far seems to be hypoglycemia. *It cannot be emphasized too strongly that there are no controlled studies regarding the use of this drug.* Thioctic acid allegedly is efficacious even after hepatic and/or renal necrosis has begun. My sense of the current literature regarding this toxin and this antidote does not suggest that you do not use it. Some of my most respected reference source people do consider using it and I would not hesitate to use it either if I felt it was indicated. The catch is that thioctic acid is currently available only from Dr. Burton Berkson of Hobbs, New Mexico — 505/392-6581.

When I think of mushrooms I think of what one of our housestaff said to me recently. He complained that he felt at times like a mushroom because he was kept in the dark and fed road apples. Bon Appetit!!

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The original formulation had been subject to a form of misuse among street abusers known as "T's and Blues." TALWIN 50 and PBZ;* an antihistamine, would be ground up together, put into solution, and injected intravenously. The combination produced a heroin-like high. Because naloxone is a narcotic antagonist when injected intravenously, it acts to nullify any high a "T's and Blues" addict might expect from the pentazocine in a combination of TALWIN Nx and PBZ. When taken as directed orally, the naloxone component of TALWIN Nx is inactive. Thus, TALWIN Nx continues to be a safe, effective, oral analgesic for the relief of moderate to severe pain, now providing added security against misuse.

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The reformulation of Talwin 50 to Talwin Nx involved the addition of 0.5 mg naloxone to help prevent misuse by injection.

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Please see following page for Brief Summary.

Talwin® Nx® IV

Each tablet contains pentazocine HCl, USP, equivalent to 50 mg base and naloxone HCl, USP, equivalent to 0.5 mg base

Analgesic for Oral Use Only

Contraindications: Hypersensitivity to either pentazocine or naloxone

TALWIN® Nx is intended for oral use only. Severe, potentially lethal, reactions may result from misuse of TALWIN® Nx by injection either alone or in combination with other substances (See **Drug Abuse and Dependence** section.)

Warnings: *Drug Dependence* Can cause physical and psychological dependence. (See **Drug Abuse and Dependence**.) *Head Injury and Increased Intracranial Pressure* As with other potent analgesics, respiratory depressant effects of the drug may elevate cerebrospinal fluid pressure due to CO_2 retention; these effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Can obscure the clinical course of patients with head injuries; in such patients, use with extreme caution and only if deemed essential. *Usage with Alcohol* Due to potential for increased CNS depressant effects, alcohol should be used with caution. *Patients Receiving Narcotics* Pentazocine is a mild narcotic antagonist. Withdrawal symptoms have occurred in patients previously given narcotics, including methadone. *Certain Respiratory Conditions* Should be administered with caution in respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Precautions: *CNS Effect* Use cautiously in patients prone to seizures; seizures have occurred though no cause and effect relationship has been established. Therapeutic doses have in rare instances, resulted in hallucinations (usually visual), disorientation, and confusion, which cleared spontaneously within a period of hours. Such patients should be very closely observed and vital signs checked, if the drug is reinstituted, it should be done with caution since the acute CNS manifestations may recur. *Impaired Renal or Hepatic Function* Decreased metabolism of pentazocine in extensive liver disease may predispose to accentuation of side effects; it should be administered with caution in renal or hepatic impairment. In long-term use, precautions should be taken to avoid increases in dose by the patient. *Biliary Surgery* Some evidence suggests that unlike other narcotics pentazocine causes little or no elevation in biliary tract pressures; the clinical significance of these findings is not yet known. *Information for Patients* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. May cause physical and psychological dependence taken alone and may have additive CNS depressant properties in combination with alcohol or other CNS depressants. *Myocardial Infarction* Use with caution in patients with myocardial infarction who have nausea or vomiting. *Drug Interactions Usage with Alcohol* See **Warnings**. *Carcinogenesis, Mutagenesis, Impairment of Fertility* No long-term studies in animals to test for carcinogenesis have been performed. *Pregnancy Category C* Should be given to pregnant women only if clearly needed. *Labor and Delivery* Use with caution in women delivering premature infants. Effect on mother and fetus, duration of labor or delivery, need for forceps delivery or other intervention or resuscitation of newborn, or later growth, development, and functional maturation of the child is unknown. *Nursing Mothers* Caution should be exercised when administered to a nursing woman. *Pediatric Use* Safety and effectiveness in children below the age of 12 years have not been established.

Adverse Reactions: *Cardiovascular* Hypotension, tachycardia, syncope. *Respiratory* Rarely, respiratory depression. *CNS Acute CNS Manifestations* In rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours, may recur if drug is reinstituted. *Other CNS Effects* Dizziness, lightheadedness, sedation, euphoria, disturbed dreams, hallucinations, irritability, excitement, tinnitus, tremor. *Gastrointestinal* Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress. *Allergic* Edema of the face, dermatitis, including pruritus, flushed skin, including plethora. *Ophthalmic* Visual blurring and focusing difficulty. *Hematologic* Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other* Headache, chills, insomnia, weakness, urinary retention.

Drug Abuse and Dependence: *Controlled Substance* TALWIN Nx is a Schedule IV controlled substance.

Dependence and withdrawal symptoms have been reported with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision. Possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy have been reported. In prescribing for chronic use, the physician should take precautions to avoid increases in dose by the patient. Tolerance to the analgesic effect is rarely reported; there is no long-term experience with oral use of TALWIN Nx.

The amount of naloxone present (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine; however, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics. TALWIN Nx has a lower potential for parenteral misuse than the previous oral pentazocine formulation, but is still subject to patient misuse and abuse by the oral route.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

Overdosage: *Treatment* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression, parenteral naloxone is a specific and effective antagonist.

Please consult full product information before prescribing

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Selenium Intoxication — New York

ON December 27, 1983, a 57-year-old female in New York began taking a daily selenium supplement distributed by Brite Years, Inc., of Tempe, Arizona. The label on the 90-tablet bottle recommended taking one of the 150-mcg tablets daily. She took the prescribed number in addition to her usual daily vitamins, which included: vitamin C (1000 mg, plus bioflavinoids, thrice daily); vitamin A (10,000 units once daily); vitamin D (400 units once daily); vitamin E (400 units once daily); B complex (once daily); and a high-potency mineral supplement labeled as containing all 72 trace elements in undefined quantities, as well as calcium, magnesium, phosphate, potassium, zinc, iron, manganese, and iodine. She consumed at least one vitamin C tablet (1000 mg) simultaneously with the selenium supplement.

Approximately 11 days after starting the selenium supplement, the patient noted marked hair loss limited to her scalp, which progressed over a 2-month period to almost total alopecia. Two weeks later, she noted white horizontal streaking on the fingernail of her left fifth digit, tenderness and swelling on the fingertip, and purulent discharge from the fingernail bed. This progressed over a 3-week period to involve all fingernails. The patient subsequently lost the entire fingernail of her left fifth digit. In addition, she experienced periodic episodes of nausea and vomiting, a sour-milk breath odor, and increasing fatigue. In January, she consulted a dermatologist for her hair loss and nail changes and was treated with oral erythromycin for paronychia. Her alopecia was attributed to emotional stress following the death of her husband a year earlier.

On March 11, 1984 she heard on the radio that the selenium tablets distributed by Brite Years, Inc., were being recalled because of superpotency. She stopped taking the tablets and consulted her internist. She had consumed 77 of the 90 tablets. A serum selenium level from March 15 was reported as 528 ng/ml, approximately four times the normal levels for the U.S. population.[1]

The distributor voluntarily recalled the product when analysis of the selenium tablets from one lot revealed a selenium level of 27.3 mg per tablet (182 times higher than labeled). The implicated tablets were reportedly manufactured by Superior Health Vitamin and Health Foods in Deer Park, New York, for the distributor. These tablets were part of approximately 250 bottles distributed to 39 accounts in 15 states (Alaska, Alabama, Arizona, Arkansas, California, Iowa, Missouri, Montana, New York, Ohio, Oregon, Pennsylvania, Texas, Utah, and Virginia) from four distribution lots (codes 012163, 016213, 301216, and 12161). Subsequent analyses of tablets from all four implicated distribution lots have contained 25 mg of sodium selenite and 4 mg-5 mg total of elemental and/or organic selenium. Analysis of tablets taken from the symptomatic woman in New York found 31 mg of total selenium per tablet.

Reported by R Jensen, DO, W Closson, PhD, Brunswick Hospital, Amityville, R Rothenberg, MD, State Epidemiologist, New York State Dept of Health; Emergency and Epidemiological Operations Br, Brooklyn District Office, U.S. Food and Drug Administration; Cancer Prevention Studies Br, Div of Cancer Prevention and Control, National Cancer Institute; Office of the Director, Epidemiology Program Office, CDC.

Editorial Note: Selenium is widely, though irregularly, distributed in soil, forages, and grains and has many commercial uses. Human intake of selenium comes mainly from cereal, fish, and meat in the diet and, in residents of one city studied, averaged 81 mcg per day.[2] While there is no established recommended daily allowance, the proposed adequate and safe intake of selenium in adults is 50 mcg-200 mcg daily.[3] Until lately, there were no well-documented cases of human selenium toxicity. A recent study reported a number of villages in the People's Republic of China where high percentages of individuals had nail and hair loss, dermatitis, nausea, garlic odor on their breath, fatigue, irritability, and hyperreflexia.[4] Individual daily dietary selenium intake in this area ranged from 3.20 mg to 6.69 mg (averaged 4.99 mg), and whole blood levels of selenium ranged from 1300 ng/ml to 7500 ng/ml (average 3200 ng/ml).*

The signs and symptoms exhibited by the New York woman were almost certainly due to selenium intoxication. The estimated cumulative dose of selenium she ingested over the 77 days was 2.387 mg. Her toxicity was probably minimized by the simultaneous ingestion of large doses of vitamin C. Vitamin C reduces selenite to elemental selenium that is poorly absorbed.

This incident demonstrates that excessive doses of trace elements can have toxic effects. Implementation of improved quality-control measures in the manufacture of these food supplements could help alleviate problems of this nature in the future. With the general increase in use of vitamin and mineral supplements in this country, the public and the medical community should be aware of the potential for toxicity.

* Whole blood selenium measurements are approximately 30% higher than serum selenium.

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Psychiatric Staff: 16
Programs: Adult and Adolescent Psychiatric

For further information about Charter Hills or admission procedures, contact:

Medical Director:
William R. Bodner, Jr., M.D.
Hospital Administrator: Harold Small

Charter Mandala Hospital

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Winston-Salem, North Carolina 27104
(919) 768-7710

Beds: 72
Psychiatric Staff: 12
Programs: Adult and Adolescent Psychiatric; Adult and Adolescent Addictive Disease

For further information about Charter Mandala or admission procedures, contact:

Medical Director: Bruce W. Rau, M.D.
Hospital Administrator: Harold Small

Charter Pines Hospital

3621 Randolph Road
Charlotte, North Carolina 28211
(704) 365-5368

Beds: 60
Programs: Adult and Young Adult Psychiatric

Scheduled to open in February 1985

For further information about Charter Pines contact:

Hospital Administrator: Stan Hilliard

Charter Northridge Hospital

400 Newton Road
Raleigh, North Carolina 27609
(919) 847-0008

Beds: 66
Programs: Adult and Adolescent Addictive Disease

Scheduled to open September 1984

Other Programs: Adult Outpatient Services

For further information about Charter Northridge contact:

Hospital Administrator: Tony Mobley

CHARTER MEDICAL CORPORATION

Infant Botulism — Massachusetts

A previously healthy 5-month-old male infant was admitted to a Massachusetts hospital in November 1983 with progressive lethargy and loss of developmental milestones over 3 weeks, constipation for 12 days, and poor suck and feeding. He had been breast-fed, and bottled foods were added at the age of 3 months. On examination, the child was generally hypotonic with flaccid extremities, no head control, and no suck or Moro reflexes. He was alert, able to smile, and had no oculomotor weakness. An electromyogram revealed a post-tetanic facilitation pattern after stimulation at 50 Hz, compatible with infant botulism. He was initially treated with intravenous hydration and saline enemas. Naso-gastric feedings were begun on the fourth hospital day, and he improved gradually thereafter. Type B botulinal toxin and *Clostridium botulinum* were identified in a stool specimen by the Massachusetts State Laboratory.

Reported by DG Sidebottom, MD, Children's Hospital, Boston, JP Reardon, MD, MB Holmes, NJ Fiumara, MD, State Epidemiologist, Massachusetts Dept of Public Health; Enteric Diseases Br, Div of Bacterial Diseases, Center for Infectious Diseases, CDC.

Editorial Note: Infant botulism, in contrast to foodborne botulism resulting from ingestion of preformed toxin, is caused by *C. botulinum* toxin produced in and absorbed from the gastrointestinal tract, leading to neurologic manifestations. This report represents the first case of infant botulism identified in Massachusetts and the second from the New England states; the first reported case occurred in 1983 in Connecticut. Infant botulism was first identified in 1976; four states — California, Texas, Pennsylvania, and Tennessee — reported cases that year. To date, 36 states in all geographic regions, including Alaska and Hawaii, have identified cases. Between 1976 and 1983, 395 cases were reported to CDC. Patients' ages ranged from 2 to 38 weeks, and 204 (53%) were male; most were hospitalized, and 11 died. Type A botulinal toxin was identified in 50% of the cases; type B, in 49%; and types F and B/F, in one case each.

A case-control study performed by the California Department of Health Services in 1976-1978 showed that infants with type B botulism were more likely than controls to have been fed honey, and type B spores were identified in implicated honey samples.[1] This is the only exposure that is a clearly defined risk factor for cases of infant botulism, and CDC has recommended that honey not be fed to infants under 1 year of age.[2] In a 1976-1980 epidemiologic study of infant botulism cases reported through CDC's surveillance system from states other than California, 96 infant botulism patients were compared with infants in the general population; infant botulism patients tended to have higher birth weights, and their mothers tended to be older and better educated.[3] Seventy percent of the botulism patients were predominantly breast-fed.

For patients in whom the diagnosis of infant botulism is considered, physicians should collect stool specimens for toxin testing and culture and should contact their state health departments for processing specimens. Treatment is mainly supportive, with gradual recovery in most cases. Enemas may be given to help eliminate toxin from the gastrointestinal tract. The roles of botulinal antitoxin and antimicrobials in treatment are unclear.

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Characteristics of Emergency Medical Services Providers in Rural Areas Who Seek Advanced Training

Theodore W. Whitley, Ph.D., Sandra S. Landis, R.N., and E. Jackson Allison, Jr., M.D./M.P.H.

THE growth and development of emergency medical services in the United States during the last two decades have been documented.[1, 2] Major advances in the development of training courses and textbooks have been made, and a system for registering emergency medical technicians (EMTs) has been established.[3] As a result of the initiative of the federal government,[4] emergency medical services are being provided by larger numbers of well-trained individuals operating from well-equipped vehicles. However, little has been reported about the personal characteristics of these individuals or their motivation for becoming emergency care providers. Therefore, the purpose of this article is to describe a group of people who have been trained to provide pre-hospital emergency care in eastern North Carolina and some aspects of their training process.

The passage of the Emergency Medical Services Systems Act of 1973 was a major cause of the rapid expansion of emergency medical services during the past decade. This legislation, which provided funds for planning emergency medical services, implementation of basic life support services, and implementation of advanced life-support services,[2] permitted emergency medical systems to become more sophisticated. In addition, the 81-hour training course for EMTs available from the National Highway Traffic Safety Administration (NHTSA) of the United States Department of Transportation has become more widely accepted, and the National Registry of Emergency Medical Technicians has developed a system for classifying EMTs on the basis of their training and competence.[1]

The three classifications used by the National Registry, which correspond to the classifications identifying training programs developed by NHTSA, are EMT, EMT-Ambulance (EMT-A), and EMT-Paramedic (EMT-P).[1] Individuals in the first two classifications have completed the NHTSA program, but individuals certified at the EMT-A level have passed a certifying examination administered by the National Registry. Individuals certified at the EMT-P level by the National Registry have satisfactorily completed a course covering advanced emergency care procedures and passed a certifying examination. Due to the advanced training provided in programs beyond the EMT-A level, these programs frequently are referred to as advanced life support (ALS) training programs.

North Carolina does not use the National Registry classification system. In fact, certification by the National Registry is not required in North Carolina. While some states do use the National Registry examination for certification at the state level, other states, including North Carolina, require individuals to successfully complete an examination developed and administered by a state agency. EMTs certified in North Carolina may seek National Registry certification if they wish.

A comparison of the classification systems used by the National Registry and by North Carolina is presented in table 1, as well as a brief description of the training requirements for certification at each level in North Carolina. Individuals who complete the basic level of training in North Carolina are called Emergency Medical Technicians (EMT), but their training corresponds to that of an EMT-A in the National Registry system. Also, the training required at the EMT-P level in North Carolina corresponds to that required by the National Registry. However, North Carolina has created a third certification level, Emergency Medical Technician-Intermediate, or EMT-I.[5] Examination of table 1 reveals that individuals certified at this level have completed a training program of at least 30 hours beyond that required for EMT certification and are qualified to initiate intravenous fluid therapy, to perform esophageal obturator airway intubation, and to withdraw blood for laboratory tests.

Despite the rapid development of emergency medical services at the national level, the majority of emergency care in rural eastern North Carolina is still provided by volunteer rescue squads or volunteer emergency medical services.[6] These groups, although committed to providing quality care, have little time for completing grant applications and little experience in seeking funds from external sources such as government agencies or private foundations. Consequently, funds for developing and implementing training programs have been scarce. In addition, the small number of communities supporting large medical centers has contributed to the difficulty encountered in providing training at all three levels and has made desired levels of medical direction difficult to attain.

During the past five years, many medical and nonmedical groups have worked together to obtain the finan-

From the Department of Emergency Medicine, East Carolina University School of Medicine, Greenville 27834.

TABLE 1

The relationship between the training programs for emergency medical technicians prescribed by the National Registry of Emergency Medical Technicians and the North Carolina Board of Medical Examiners*

National Registry	North Carolina	North Carolina Requirements			EMS Project Requirements		
		Course Hours	Course Content	Examinations	Course Hours	Course Content	Examinations
EMT-A†	EMT	71 didactic 10 clinical 81 total	EMS System Extrication Determining the Extent of Injury Transfer Techniques	Written: 160 items Practical Skills: 1. assessment 2. splinting 3. CPR 4. vital signs 5. airway 6. spinal immobilization (6 stations total)	No course offered		
	EMT-I	27 total	Terminology & Professionalism Cardiovascular System Shock & Fluid Therapy Respiratory System-EOA Portion 6 successful IV starts in classroom 10 successful IV starts in clinical	Written: 160 items Practical Skills:‡ (6 EMT skills repeated) Additional Practical Skills: 1. IV insertion 2. venipuncture for blood withdrawal 3. EOA insertion (9 stations total)	111 didactic 30 clinical 141 total	Terminology & Professionalism Shock & Fluid Therapy Skills: 1. IV 2. EOA 3. MAST Systems Review Assessment of Pathologic States	Pretest: 60 items Posttest: 60 items Practical Skills: 1. IV & fluid therapy 2. venipuncture for fluid therapy 3. MAST 4. case study
EMT-P	EMT-P	200 lecture, practical and evaluation 218 clinical 418 total	General Pharmacology Respiratory System Central Nervous System Soft Tissue Injuries Musculoskeletal System Medical Emergencies Obstetric/Gynecology Emergencies Management of the Emotionally Disturbed Rescue Techniques Telemetry & Communications	Written: 160 items Practical Skills: (6 EMT & 3 EMT-I skills repeated) Additional Practical Skills: 1. endotrachael intubation 2. medication administration 3. defibrillation (12 stations total)	180 didactic 4 self-study weeks (at 15 hrs/wk) 150 clinical and field 390 total	Terminology & Professionalism Skills: 1. Airway Mgt. 2. EKG recording Dysrhythmia Interpretation Pharmacology Assessment & Field Intervention Management of Cardiac Dysrhythmias Rescue Techniques Communication of Vital Information Review	Pretest: 60 items Posttest: 100 items Practical Skills: (4 EMT-I Skills repeated) Additional Practical Skills: 1. defibrillation 2. pharmacology 3. endotrachael intubation 4. case study (8 stations total)

* The North Carolina Office of Emergency Medical Services is the agency responsible for the administration of ALS training programs for Emergency Medical Technicians and serves as liaison between providers and the Board of Medical Examiners.
† Any certified EMT from any state may obtain this classification by passing an examination administered by the National Registry.
‡ Testing of practical skills at the EMT-I and EMT-P levels is the responsibility of the local medical director of the training program.

cial resources necessary to expand emergency medical services in eastern North Carolina. One result of these efforts was the procurement of a $500,000 grant from the United States Department of Health and Human Services,[7] which was awarded in 1980 for one year. Matching funds from local sources doubled the amount of money available to $1,000,000. These funds were used primarily to purchase communications equipment as well as equipment for emergency departments and ambulances.

Public awareness of emergency medical services generated by community efforts, physician involvement, and the availability of grant funds led to an increase in the number of EMTs who wished to obtain certification at the EMT-I level. The Emergency Medical Services (EMS) Project was established by the East Carolina University School of Medicine (ECUSOM) in 1979 to help provide this training. The project is administered by the Department of Emergency Medicine at ECUSOM and provides education, training, and community support in the 29-county region of eastern North Carolina.

Program

The ALS training programs developed by the EMS Project as outlined in table 1 are designed to provide quality training which meets both state and federal standards. The Department of Emergency Medicine at East Carolina Uni-

versity School of Medicine is very sensitive to the need to develop ALS programs that are responsive to community needs and permit people in the communities to manage them. As a result, the initial efforts of the project staff were directed not only toward the development of a curriculum, but also toward informing physicians, hospital administrators, nurses, and other support staff about the training of EMT-Is and the kinds of services they could provide. This informational process was, and still is, considered particularly important because hospitals and their medical staffs must be willing to accept responsibility and liability for the care provided by EMT-Is under their sponsorship. In addition, medical personnel from the sponsoring hospitals have served to augment the core faculty enlisted by the EMS Project to teach in the program and have played an active role in the training programs initiated by rescue squads in their communities.[6]

The curriculum used to train EMT-Is has been described in detail.[6] Briefly, the curriculum is based on a course guide available from the United States Department of Transportation.[8] Four modules from this guide have been adapted for use by project faculty: a) The Emergency Medical Technician, his role, responsibility, and training, b) Human systems and patient assessment, c) Shock and fluid therapy, and d) The respiratory system. The course consists of 141 hours divided into 75 hours of didactic instruction, 30 hours of precepted clinical experience, 27 hours of EMT recertification instruction, 3 hours of ALS skills examination, and 6 hours required to take the certification examination administered by the North Carolina Office of Emergency Medical Services.

In addition to the core faculty, standard curriculum, and precepted clinical experience, several other steps are taken to insure that EMT-Is trained by the EMS Project will be able to provide appropriate care. For example, a written pretest designed to assess knowledge and skills which should have been acquired during training for certification as an EMT and through experience as an EMT is administered to each prospective trainee. The potential candidate is then screened by members of the local medical community, members of the staff of the sponsoring hospital and members of the rescue squad requesting the training program. Each trainee who completes the program also takes a posttest and is interviewed by the same panel. The purpose of the second interview is to determine which trainees should be recommended to the North Carolina Board of Medical Examiners as candidates for the certification examination administered by the Office of Emergency Medical Services.

Characteristics of Providers

Individuals willing to undergo the training required to become certified at the EMT-I level and willing to assume the responsibility for providing pre-hospital care appropriate to this level of training are a special group. The remainder of this paper is devoted to describing some of the personal characteristics of individuals from eastern North Carolina who seek to acquire ALS skills and to explore some possible reasons for their willingness to assume the responsibility for providing emergency care.

In general, the trainees enrolled in the EMS Project during the past two years are young. Their ages range from 18 (the statutory limit) to 59 years with 83.1% under 40 and 3.4% 50 years old and older. The mean age is 31.3 years and the median age is 29.4 years. This age range is reflected in the amount of EMS experience of the trainees. While the range of experience extends from less than one year to 14 years, the mean is only 3.6 years and the median is 2.9 years. In fact, 2.4% of the trainees have less than one year of experience, 78.5% have one to five years, and 97.6% have less than 10 years.

The educational attainment of the trainees also reflects their relatively young age. Specifically, 53.4% have a high school degree or less education, and only 12.5% have completed 16 or more years of education. However, 29.4% of the trainees have attended a college or university for some period of time, and a surprisingly small percentage (13.9%) have attended a technical institute or community college. Only 2.3% of the trainees have not earned a high school diploma, and only 1.8% have obtained a high school diploma via the Tests of General Education Development. As would be expected from the percentage of trainees in each category, the mean educational achievement is 14.7 years; the median is 12.5 years.

The trainees are employed in a variety of occupations (table 2). The relatively high percentage of EMS professionals may be perplexing until two facts are considered. First, as might be expected, units employing EMS professionals have been quick to seek training through the EMS Project. Second, these units are interested in providing ALS training for new employees as quickly as possible. Therefore, several squads employing EMS professionals have requested two or three training programs. As more squads and services comprised of volunteers receive training, the percentage of EMS professionals will reflect the

TABLE 2
Distribution of EMS Providers Enrolled in the EMT-I Training Program by Occupation

Occupation	Frequency	Percent
Fire Fighter	15	6.8
Law Enforcement	10	4.5
Nurse	14	6.3
Teacher	4	1.8
Farmer	4	1.8
Industry/Commerce	34	15.4
Executive/Manager	7	3.2
EMS Professional	70	31.7
Other (unspecified)	4	1.8
Other Health Field	8	3.6
Military	7	3.2
Student	4	1.8
Housewife	12	5.4
Clerical	6	2.7
Government Employee	3	1.4
Clergy	1	0.5
Mechanical/Maintenance	4	1.8
Barber	1	0.5
Retired	1	0.5
Engineer	1	0.5
Journalist	1	0.5
Unknown	10	4.5
Total	221	100.0

actual composition of ALS providers in the region more accurately.

In a similar manner, the percentage of full-time EMTs (37.4%) in relation to volunteer EMTs (55.9%) and part-time EMTs (6.6%) is somewhat unrepresentative of the region. These data should change over time, however, for the reasons mentioned in the preceding paragraph. A dramatic increase in the number of full-time paid EMTs in the region seems unlikely in the immediate future.

The most appealing explanation for the willingness of the individuals described in the preceding paragraphs to obtain ALS training is the fact that they will be providing services in the communities in which they live. In many instances, they will be acquainted with the people receiving their services. Whatever their reasons, these individuals are willing to make a substantial time commitment to become EMT-Is.

This time commitment begins with the initiation of training. As noted previously, the training program consists of 141 hours. Classes are held at night to accommodate trainee work schedules. The potential drawback to this schedule is that trainees, particularly volunteers, frequently voice their expectation that all learning will occur during classes. This impression is probably compounded by the relative youth of the trainees and the fact that many have had no exposure to higher education. Consequently, the only assignments that require time outside of class involve reading the required textbook. Since 83% of the trainees known to have taken the state certification examination passed it, these potentially troublesome educational factors apparently can be overcome.

The time commitment does not end with certification. Members of rescue squads must respond to calls during work hours. Moreover, these calls may be to locations at some distance from the EMT's place of work. Except for EMS professionals, EMTs must complete the tasks at their workplace when they return. Finally, calls at night reduce the time available for leisure and/or family activities.

Conclusion

A group of young men and women with diverse educational and occupational backgrounds is willing to assume responsibility for providing emergency medical services in communities in rural eastern North Carolina. They are also willing to make a significant time commitment to secure the training required to provide these services. The results of the state certification examination indicates that participants in the EMS Project have acquired the skills taught at the EMT-I level and can apply what they have learned.

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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

August 14

Malpractice Awareness — STAT
Place: Charlotte
Info: Wayne Parker. 919/828-9334

August 15

Electrolytes/Arterial Blood Gases/Fluid Balance
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St, Sanford 27330. 919/774-4100, ext 394

August 21

Malpractice Awareness — STAT
Place: Goldsboro
Info: Wayne Parker. 919/828-9334

August 24, 26

Summer Urology Conference
Place: Winston-Salem
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

September 9-12

Basic Clinical Teaching Skills
Place: Rougemont
Credit: 20 hours Category I and AAFP
Info: Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571.

September 9-13

Clinical Skills Workshops and Review
Place: Winston-Salem
Credit: 31 hours Category I
Fee: $395
Info: Elizabeth B. Philp, Department of Family Medicine, Bowman Gray School of Medicine, Winston-Salem 27103.

September 11

New Developments in Clinical Medicine
Place: Fayetteville
Credit: 7 hours AAFP
Info: Mary Henley. 919/323-1152.

September 21

Sixth Annual Health Law Forum
Place: Greenville
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200.

September 21-22

New Advances in the Treatment of Sickle Cell Disease
Place: Wrightsville Beach
Credit: 8 hours Category I
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878.

September 28-29

Adolescent Health Issues: Challenges for the 1980s
Place: Durham
Credit: 9 hours Category I
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878.

October 1-5

Nuclear Magnetic Resonance for the Imaging Team
Place: Winston-Salem
Credit: 30 hours Category I AMA
Fee: $500
Info: Richard Witcofski, Ph.D., Department of Radiology, Bowman Gray School of Medicine, Winston-Salem 27103.

October 1-5

Microsurgery Workshop
Place: Durham
Credit: 40 hours Category I AMA
Info: Jackie Brooks, Box 3372, Duke University Medical Center, Durham 27710. 919/684-3347

October 3

Practical Solutions for Common Medical Problems
Place: Research Triangle Park
Credit: 6 hours Category I AMA
Info: Kathy Hundley, Educational Services Coordinator, Burroughs Wellcome, Research Triangle Park 27709. 919/248-4904

October 3-4

24th Annual Charlotte Postgraduate Seminar
Place: Charlotte
Credit: 16 prescribed hours AAFP
Info: J. Lewis Sigmon, Jr., M.D., Box 32861, Charlotte 28232. 704/331-3172

October 5-7

Practical Problems in Arthritis Management
Place: Wrightsville Beach
Credit: 9 hours Category I AMA
Fee: $65
Info: NC Chapter of the Arthritis Foundation, Box 2505, Durham 27705. 1/800/672-0949

October 13-14

Radiology Mini-Course in Abdominal Imaging
Place: Durham
Credit: 10 hours Category I AMA
Info: Cindi Easterling, Box 3108, Duke University Medical Center, Durham 27710. 919/684-6878

October 24-27

Fall Seminar, American Academy of Clinical Anesthesiologists
Place: Asheville
Credit: 11 hours Category I AMA
Info: AACA, Knoxville, TN 37919-1691. 615/588-6279

October 26-27

Psychopharmacology: Practical Drug Treatment of Psychiatric Disorders
Place: Chapel Hill
Credit: 10 hours Category 1 AMA
Fee: $125
Info: Nancy Williams, Department of Psychiatry, UNC School of Medicine, Chapel Hill 27514. 919/966-4738

October 26-27

Advanced Cardiac Life Support Instructors Course
Place: Winston-Salem
Credit: 20 hours Category I AMA and ACEP
Fee: $250
Info: Earl Schwartz, M.D., Emergency Medicine, Bowman Gray School of Medicine, Winston-Salem 27103.

November 1-2

Current Topics in Urology
Place: Chapel Hill
Credit: 13 hours Category I AMA
Fee: $125
Info: Barbara Judd, 428 Burnett-Womack Building 229H, Chapel Hill 27514. 919/966-2571

November 11-14

Advanced Clinical Teaching Skills
Place: Rougemont
Credit: 20 hours Category I AMA and AAFP
Info: Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

OUT OF STATE

August 12-17

Symposium on the Surgical Treatment of Cancer
Place: Orlando, FL
Credit: 20 hours Category I AMA
Info: C. Easterling, Box 3108 Duke Hospital, Durham 27710. 919/684-6878

September 6-8

Doppler Echocardiography
Place: Charleston, SC
Credit: 24 hours Category 1
Fee: $350
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103. 919/748-4450.

September 13-15

Advanced Applied Ultrasound in Obstetrics
Place: Myrtle Beach, SC
Credit: 12 hours Category 1
Fee: $350
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103. 919/748-4505.

September 20

Use of Computers in the Medical Office
Place: Johnson City, TN
Credit: 6 hours Category 1 AMA
Fee: $60
Info: Sue Hutchinson, Quillen-Dishner College of Medicine, Johnson City, TN. 615/928-6426, ext. 204

October 12

Selected Topics in Pediatrics
Place: Norfolk, VA
Info: Jean E. Shelton, M.D., Children's Hospital of the King's Daughters, 800 West Olney Road, Norfolk, VA 23507. 804/628-3798

October 18-25

Review of Clinical Chemistry Seminar
Place: San Diego, CA
Credit: 40 hours Category I AMA
Fee: $315
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

October 20-27

4th Diving Accident and Hyperbaric Oxygen Treatment
Place: Grand Cayman, BWI
Credit: 26 hours Category I AMA, AAFP, ACEP
Info: Cindi Easterling, Box 3108, Duke University Medical Center, Durham 27710. 919/684-6878

October 22-26

Postgraduate Course in Diagnostic Imaging
Place: Bermuda
Credit: 25 hours Category I AMA
Fee: $495
Info: Jacqueline D. Wright, Box 3808, Duke University Medical Center, Durham 27710. 919/681-2711

November 13

Divorce, Child Custody and the Family
Place: Johnson City, TN
Info: Sue Hutchinson, Quillen-Dishner College of Medicine, Johnson City, TN. 615/928-6426, ext. 204

Three Studies in Progress at UNC in Search of Patients

• Drs. John T. Sessions, Jr. and Eugene M. Bozymski of the Division of Digestive Diseases and Nutrition at the UNC School of Medicine are joining with clinical investigators at several other academic study centers in a clinical trial for the evaluation of Flagyl (metronidazole) as a therapeutic agent in patients with Crohn's disease (ileitis). The purpose of the study is to investigate the safety and efficacy of Flagyl as an alternative to prednisone and sulfasalazine. Recent trials have suggested that Flagyl is an effective therapeutic agent in the treatment of Crohn's disease.

Study participants will receive free care and medication and will be reimbursed for travel expenses. Those patients who participated in the ealier National Cooperative Crohn's Disease Study are eligible provided they meet study criteria.

If you have a patient with moderately active Crohn's disease whom you would like to refer, we would be pleased to evaluate him/her for participation in this four-month study. During the study you will be kept informed of your patient's progress and upon completion of the study your patient will be returned to your care.

For further information please contact either Dr. Sessions or Dr. Bozymski at 919/966-2511 or Alice Rupen, Crohn's Study Coordinator, at 919/966-5800.

• Drs. Eugene Bozymski and Roy Orlando are conducting two clinical studies at the University of North Carolina at Chapel Hill. One study concerns the efficacy and safety of Sucralfate suspension in the treatment of symptomatic reflux esophagitis. Patients with symptoms of heartburn and endoscopic/histologic evidence of esophagitis are eligible for this study. We are also studying the efficacy of oral prostaglandins on benign gastric ulcer healing. These two studies are being conducted without cost to the patient. If you have any patients who might be suitable and interested, please contact Dr. Eugene Bozymski, Dr. Roy Orlando, or Debbie Buddin, MSN at the UNC School of Medicine 919/966-2511. At the completion of the study patients will be returned to the care of their personal physician.

Classified Ads

PHYSICIAN ASSISTANTS — Would a Physician Assistant be of benefit to your practice? The North Carolina Academy of Physician Assistants responds promptly to physician inquiries. Contact: Paul C. Hendrix, P.A.-C, Chairman, Employment Committee, 708 Duluth Street, Durham, North Carolina 27705. Telephone: 919/684-6101.

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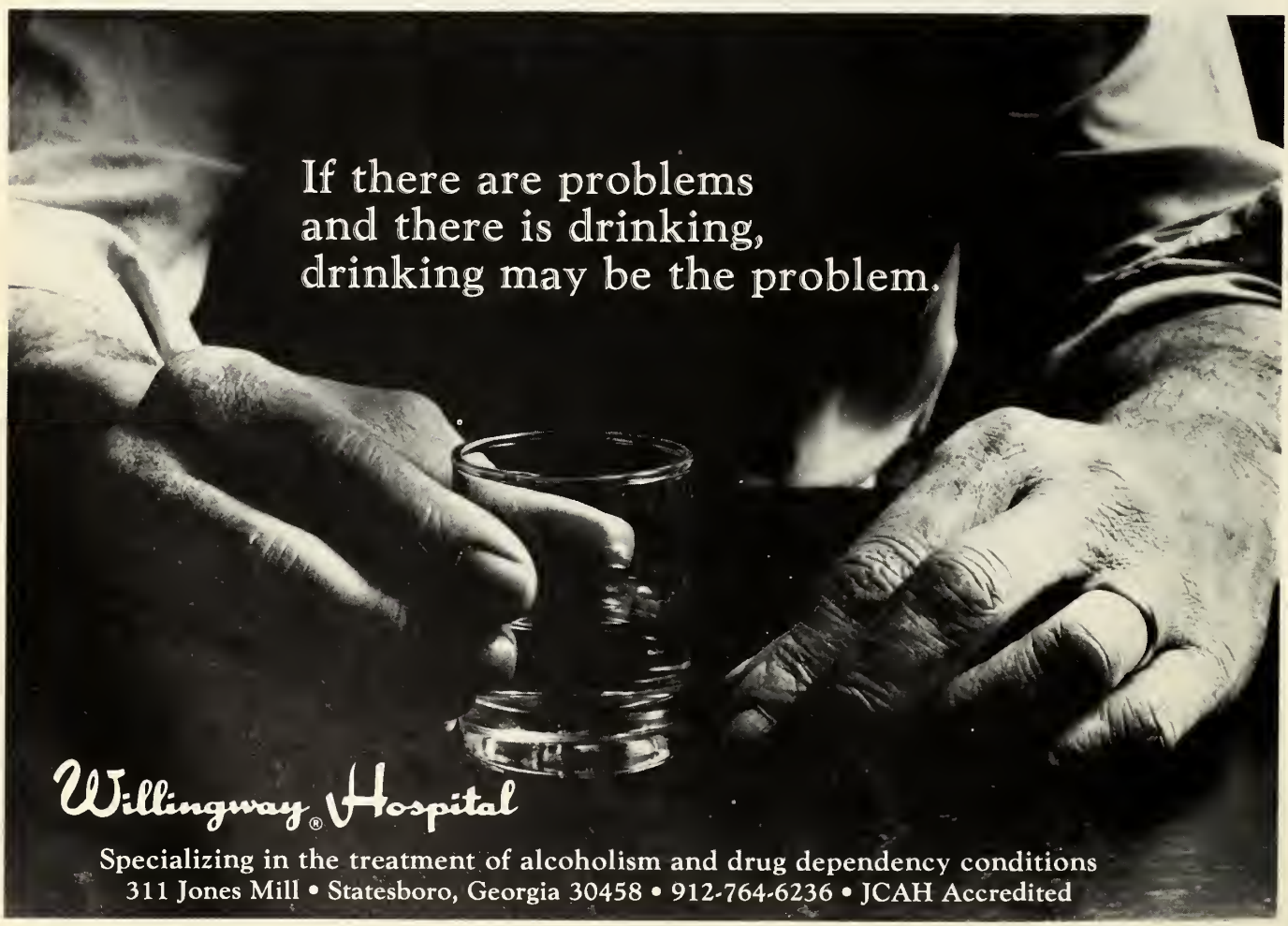
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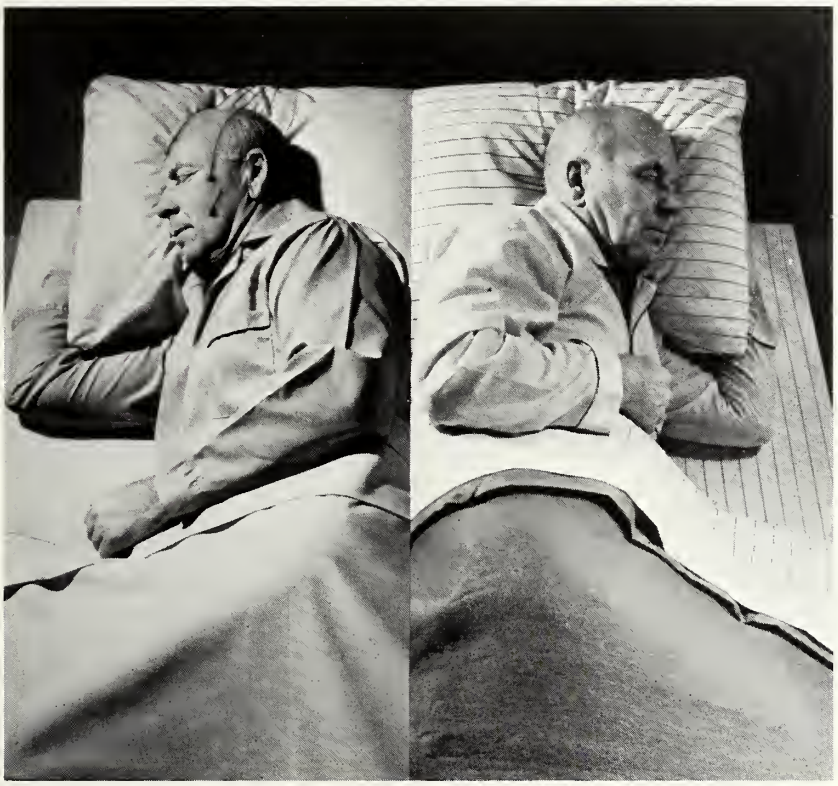
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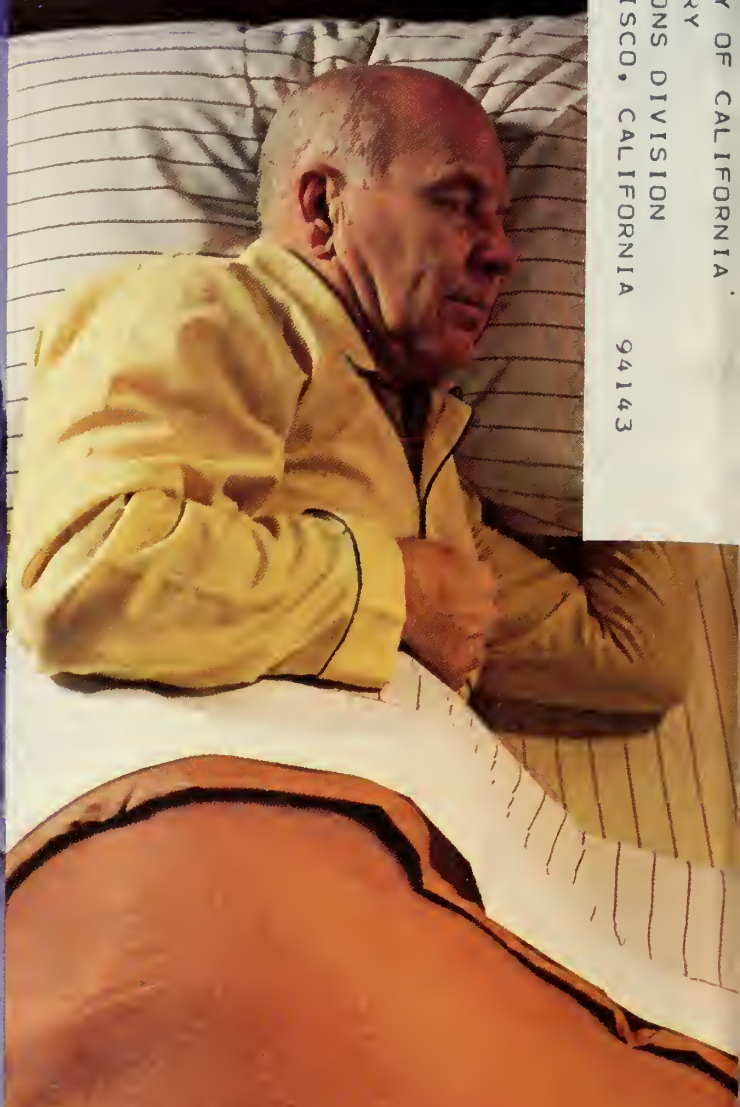
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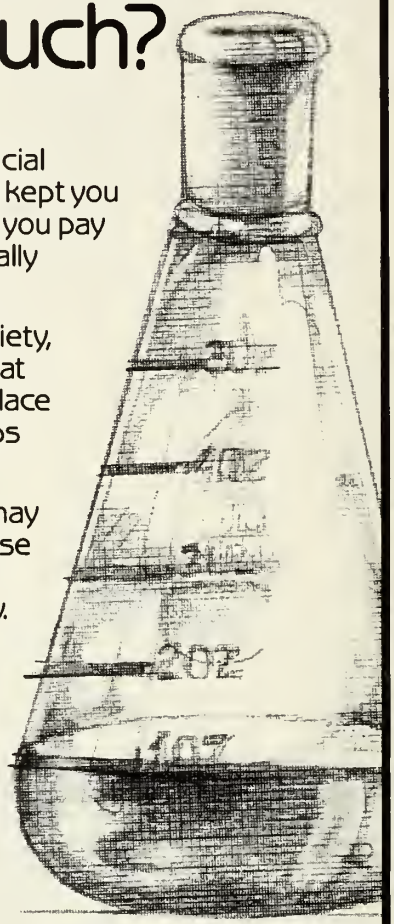
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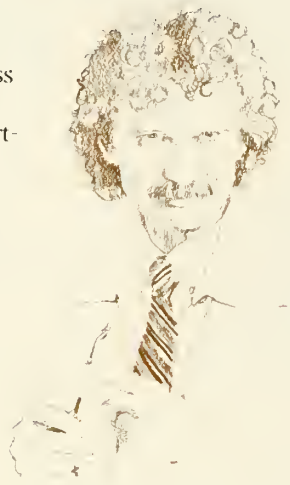
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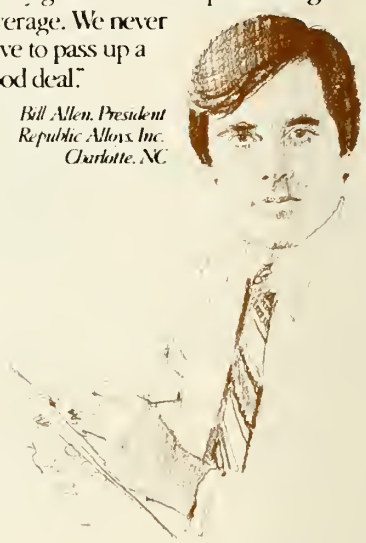
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SCIENTIFIC ARTICLE

Update — The Sudden Infant Death Syndrome in North Carolina

Marianna M. Henry, M.D., Evangeline S. Getzen, M.P.A., Kay A. McNeill-Harkins, R.N., M.P.H., and Gerald L. Strope, M.D.

• *An update on the occurrence of SIDS in approximately 150 North Carolina infants each year.*

EACH year in North Carolina 140-160 infants die of sudden infant death syndrome (SIDS). Many additional infants present with apnea and are thought to be at increased risk for sudden, unexplained death. Professionals from several disciplines are currently working with families of SIDS victims and high risk infants in this state. The purpose of this report is to review briefly the epidemiology and etiology of SIDS, the management of SIDS deaths, the evaluation of infants with apnea, and the options available to physicians and parents of infants thought to be at increased risk of SIDS in North Carolina.

Epidemiology

The sudden infant death syndrome is defined as the sudden death of any infant which is unexpected by history and unexplained after a postmortem examination. Approximately 7,000 deaths each year in the U.S. are attributable to SIDS, making this syndrome the greatest single cause of death in the age group from one month to one year. SIDS accounts for nearly one third of all postneonatal infant deaths.

Several characteristics of SIDS emerge from available epidemiologic data. The peak incidence occurs at age two to four months with relative sparing of the infant less than one month old. Ninety percent of SIDS deaths occur during the first six months of life. A seasonal pattern is suggested by an increased incidence during the winter months. Affected infants are generally perceived as well; however, many have had recent mild upper respiratory infection. Death tends to occur at night while the infant sleeps but may occur during the day under a variety of other circumstances.

The incidence of SIDS in North Carolina during 1979-82 was 1.78/1000 live births, approximately the same as the national incidence. The sex and race related incidences of SIDS for 1979-82 are shown in table 1. Males were affected more commonly than females (male:female 1.43:1). The incidences in the black and Indian populations were greater than in the white population (2.70, 2.88, and 1.33/1000 live births, respectively). These race related incidences are similar to those reported by Blok[1] except that the incidence in the Indian population during 1979-82 was considerably lower than he reported in North Carolina during 1972-74 (2.88 vs 6.56/1000 live births). The small number of Indian births each year and inaccurate racial designation based on incomplete family information may contribute to these differences in SIDS rates. The effect of socioeconomic background on these differences in race related incidence is unknown. The incidence of SIDS by county during 1979-82 is shown in figure 1. County incidences ranged from 0-6.6/1000 live births. (North Carolina SIDS data are provided by the North Carolina SIDS Project Office. Data are based on autopsy information available in 95% of cases primarily from the office of R. Page Hudson, M.D., Chief Medical Examiner of North Carolina.)

Risk Factors for SIDS

Numerous maternal and infant risk factors for SIDS have been identified. Maternal risk factors include: maternal age of less than twenty years, single marital status, delayed initiation of prenatal care or few prenatal visits for medical care, chronic disease during pregnancy, low socioeconomic status, smoking, and heroin addiction. Known infant risk factors relate primarily to prematurity and family history of SIDS. Specific risk factors include: prematurity (7/1000 live births), multiple births (3.8/1000 for twins and 8.3/1000 for triplets), sibling of SIDS (20/1000), and repetition of SIDS in multiple births (42/1000). The risk to cousins of SIDS victims is thought to be about the same as the risk for the general population (2.2/1000).[2]

Pathogenesis

Though the etiology of SIDS remains obscure, our understanding of this disorder has broadened in recent years. Many SIDS victims are no longer considered to be normal prior to death. Approximately two-thirds of SIDS victims examined in special pathologic studies have been found to have evidence of chronic tissue hypoxia as demonstrated by hypertrophy and hyperplasia of pulmonary arterial musculature with the abnormal extension of musculature into more peripheral pulmonary arterioles, right ventricular hypertrophy, extramedullary hematopoiesis, and

From the Department of Pediatrics, The University of North Carolina, Chapel Hill 27514 and the SIDS Project Office, North Carolina Division of Health Services, Raleigh 27602.

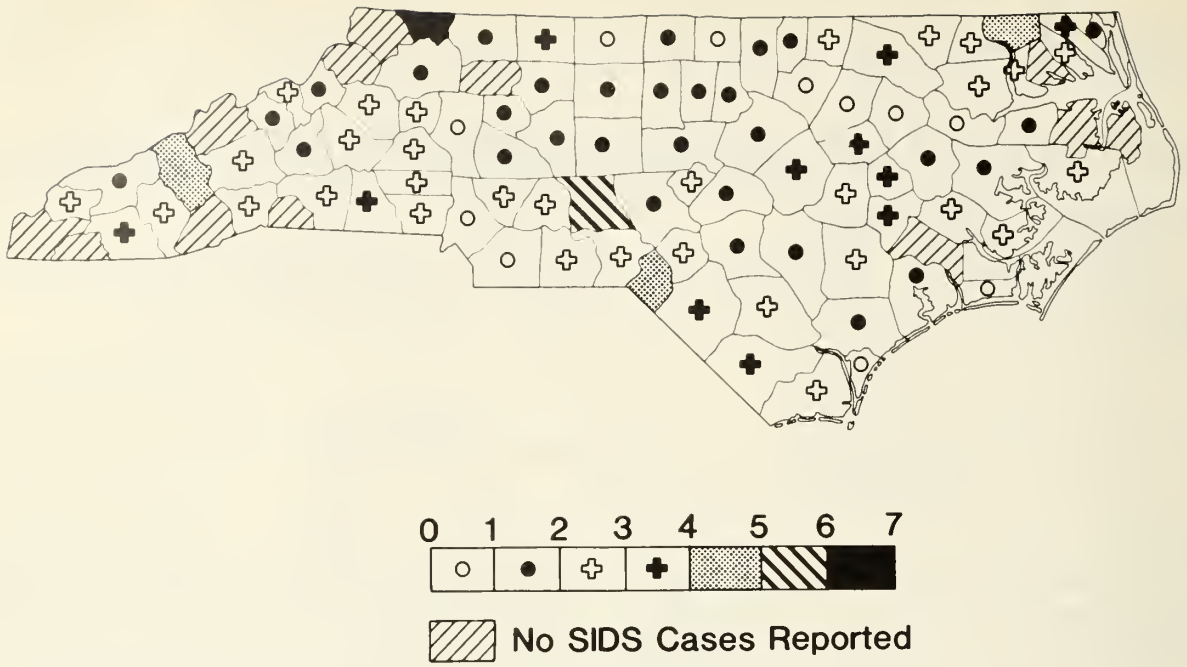


Figure 1. *County incidence of SIDS in North Carolina, 1979-1982. Incidence given as number of SIDS cases/1000 live births (n = 600).*

astroglial cell proliferation in the brain stem. This evidence suggests that some SIDS victims may experience repeated episodes of hypoxia prior to death. The mechanisms accounting for hypoxia are unclear; however, the leading hypothesis is that abnormalities in the neural regulation of respiratory and cardiovascular processes contribute to this episodic hypoxia.

Clinical support for the hypothesis that death may result from abnormalities in respiratory control comes from the observation that some SIDS victims experience repeated episodes of non-fatal apnea prior to death. Physiologic studies of infants who have survived episodes of apnea, so-called "near-miss SIDS" infants, have shown that as a group these infants have more frequent episodes of apnea, more periodic breathing, and may have an abnormal ventilatory response to administered CO_2. Future investigation of these infants, family members of SIDS victims, and animal models may ultimately yield information on specific abnormalities in respiratory control or reflex mechanisms peculiar to the developing nervous system that contribute to SIDS deaths.

Many other hypotheses explaining SIDS deaths have been proposed and later abandoned. Multiple mechanisms probably play a role in this syndrome. Current clinical and laboratory evidence suggests that gastroesophageal reflux, seizure disorders, and cardiac arrhythmias may be impor-

Table 1
Number of Sudden Infant Death Syndrome Deaths in North Carolina, 1979-1982*

Race/Sex	1979		1980		1981		1982		Total (1979-1982)	
	N†	Rate‡	N	Rate	N	Rate	N	Rate	N	Rate
White	63	1.1	88	1.5	82	1.4	78	1.3	311	1.33
Male	40	1.4	55	1.9	50	1.7	53	1.8	198	1.70
Female	23	0.8	33	1.2	32	1.2	25	0.9	113	1.03
Black	85	3.4	68	2.7	56	2.3	61	2.4	270	2.70
Male	51	4.1	35	2.8	26	2.1	38	3.0	150	3.00
Female	34	2.7	33	2.7	30	2.5	23	1.8	120	2.43
Indian	5	3.2	5	3.2	4	2.6	4	2.5	18	2.88
Male	4	4.9	3	3.9	2	2.6	2	2.5	11	3.48
Female	1	1.4	2	2.5	2	2.6	2	2.5	7	2.25
Total	153	1.8	161	1.9	142	1.7	144	1.7	599	1.78
Male	95	2.2	93	2.2	78	1.8	93	2.1	359	2.08
Female	58	1.4	68	1.6	64	1.6	50	1.2	240	1.45

* This table does not include one female infant of another race who died of SIDS in 1982.
†N = number of children who died of SIDS.
‡Rate = number of SIDS deaths/1000 live births.

tant contributing factors. The interested reader is referred to several excellent review articles for more comprehensive discussion.[3-7]

Near-Miss SIDS

The term "near-miss SIDS" has been applied to infants who experience an episode of apnea with limpness, cyanosis, or pallor and respond to vigorous stimulation or resuscitation. The term "apnea of infancy" has been proposed as a more appropriate label since "near-miss SIDS" may imply a closer relationship to SIDS than can be substantiated. Nevertheless, infants presenting with apnea between one and four months of age are presumed to be a subset of the SIDS population with similar mechanisms accounting for non-fatal and fatal episodes. Extensive evaluation of these infants may uncover associated, treatable conditions, some of which are listed in table 2. Approximately 40-50% of these infants will have subsequent episodes of apnea requiring intervention, often recurring during the stress associated with infections or immunizations.[8, 9] Available information suggests that 5-10% of these infants may ultimately die of SIDS, even when placed on home monitors.[9]

Management of SIDS and Apnea of Infancy

The medical management of a suspected SIDS episode should involve careful documentation of historical events and a detailed postmortem physical examination. Referral to the North Carolina Medical Examiners System for an autopsy is required for any unexplained infant death. The impact of an unexpected infant death can be devastating to families. Health professionals should communicate in a non-threatening manner, attempting to relieve any perceived family guilt. A timely conference to interpret autopsy findings is essential. Siblings and other caretakers should be included in modified sessions. Additional family support can be provided by the county SIDS grief counselor, a health professional specifically trained in the epidemiologic, medical, and psychosocial aspects of SIDS. This person's role is to provide families with information about SIDS, assist with the interpretation of autopsy findings, and facilitate the grieving process. SIDS parent support groups are also available in some counties. Information about county grief counselors can be obtained through the SIDS Project Office, Maternal and Child Health Branch, North Carolina Division of Health Services, PO Box 2091, Raleigh, North Carolina 27602 (1/800/662-7030).

Table 2
Disorders Associated with Apnea of Infancy

1. Infectious
   - Meningitis
   - Bronchiolitis
   - Pneumonia
   - Sepsis
2. Neurologic
   - Seizures
   - Intraventricular hemorrhage
   - Central alveolar hypoventilation
3. Respiratory
   - Obstructive lesions
4. Cardiovascular
   - Arrhythmias
   - Vascular rings
5. Gastrointestinal
   - Gastroesophageal reflux
6. Metabolic
   - Electrolyte imbalance
   - Metabolic acidosis
   - Hypoglycemia
   - Hypocalcemia
7. Other
   - Anemia
   - Prematurity
   - Idiopathic

The evaluation of an infant with apnea begins with documentation of the events surrounding the apneic episode. Information concerning the length of apnea, associated color changes, relationship to feeding, observed vomiting, potential seizure activity, other unusual symptoms, and the nature of resuscitative efforts should be sought specifically. The infant should be hospitalized for cardiorespiratory monitoring and evaluated for potentially treatable disorders as previously mentioned. Referral to a regional medical center is often needed for diagnostic studies and initiation of therapy.

Useful therapies for these infants may include: cardiac drugs, seizure medications, respiratory stimulants, therapy for gastroesophageal reflux, and surgery in selected cases. In some cases, no explanation for the episode will be discovered and home monitoring may be offered as a method of alerting parents to the occurrence of apnea or bradycardia so that intervention can be initiated promptly. In situations where the basis of an apneic event is better understood, home monitoring may be a useful adjunct to other therapeutic measures.

The success of a home monitoring program depends on appropriate parental education in the use of the monitor and infant cardiopulmonary resuscitation, provision of psychosocial support to the families, and assurance of appropriate continuing medical care. Home monitoring is usually continued until the infant has had two months without apnea alarms and is six months of age. Although appropriate studies have not been done to demonstrate that home monitoring reduces mortality, many authorities believe that the high rate of recurrence of apnea requiring intervention and subsequent SIDS deaths in this population justify the use of home monitoring until more specific therapy is available.

Home monitoring programs are available in most regional referral centers in North Carolina. Many private practitioners are also initiating home monitoring services. Data from companies supplying home monitoring services suggest that approximately 230 infants were monitored for apnea during 1983 in North Carolina.* This figure does not

* Data concerning monitored infants were obtained from the following: physicians and suppliers of home monitoring services: Cindy Lively, M.D., Bowman Gray School of Medicine, Winston-Salem; Alexander Spock, M.D., Duke University, Durham; Ross Vaughn, M.D., Wake Medical Center, Raleigh; John Wimmer, M.D., East Carolina University, Greenville; Charles Yoder, M.D., Asheville Neonatology, Asheville; Debbie Brookshire, Travenol Home Respiratory Services, Charlotte; Steve Chaucer, Medicare Supply Company, Durham; Jeff Jenkins, Glasrock Home Health Care, Raleigh; Steve Murtola, Ambulatory Services, Asheville; Matthew Recchio, Northwest Home Care, Winston-Salem; and Dave Varner, Ambulatory Services, Charlotte.

include otherwise well infants monitored as siblings of SIDS victims and may not include a small number of infants monitored with community-owned monitors.

Approximately 50% of these monitor referrals were made directly by private practitioners. The remainder were initiated by physicians in referral centers. The monthly charge for equipment and 24-hour service is about $240.00, a cost covered usually by major insurance carriers. Monitors for Medicaid patients can often be provided with the assistance of local home health agencies. We are not aware of any litigation in North Carolina concerning the use of home monitors.

Infants in the increased risk categories, such as siblings of SIDS victims and premature infants, pose special problems. At this time, no test is known which will identify infants most likely to die. The challenging care of these infants and their families involves medical evaluation of the infant, identification of family concerns, and judgment regarding the use of any therapeutic modality including home monitoring.

Conclusion

Although our understanding of the sudden infant death syndrome has increased in recent years, much remains to be learned about the etiology and ultimate prevention of these deaths. As professionals caring for families of SIDS victims and infants with apnea we need to remain aware of current concepts of pathogenesis and treatment and resources available in North Carolina to facilitate optimal care. Specialized centers for the care of infants with apnea are being developed in several major medical centers in North Carolina, as in other areas of the country. Professionals practicing neonatology, pulmonology, cardiology, gastroenterology, neurology and psychology/psychiatry are available to offer guidance in the specific evaluation and management of these infants.

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North Carolina: The Health of Our State

Ronald H. Levine, M.D., M.P.H.

• *The State Health Director's annual report on the state of the health of the state.*

FIFTY years ago this week, Dr. I. H. Manning of Chapel Hill, then President of the N.C. Medical Society, opened the Society's annual meeting with these words: "The public health should be a matter of gravest concern to the medical profession. Prevention of disease is one of the marvelous accomplishments of modern medicine and a glorious task for the profession. A death from a preventable disease should be on our conscience." That abiding interest and concern of the medical profession for the public health manifests itself each year in its receipt of the statutorily-based Conjoint Report which I am privileged to present once again. As in the past, I will highlight one topic of special interest, this year infant mortality in North Carolina. Interestingly enough, Dr. George Cooper, the Director of Preventive Medicine in North Carolina in 1934, had, according to President Manning, "called attention of the profession to the high . . . infancy death rate in this state."

First, allow me to offer a brief review of accomplishments, problems and issues of the year past. Several significant events occurred that will have an impact on tuberculosis control in North Carolina. At the request of the Department of Human Resources, the General Assembly voted to close McCain Hospital as a tuberculosis sanatorium. Thus the last tuberculosis sanatorium in this state and one of the last in the nation is no more. Nearly one-half million dollars in resulting savings were appropriated to the Department to be used to support tuberculosis control services across North Carolina. As a result of this allocation, we are now providing financial assistance for inpatient care as well as tuberculosis casefinding and management in all 100 counties of the state. Additionally, a 25-bed facility for tuberculosis patients requiring convalescent care was opened on October 1, 1983 at Cherry Hospital in Goldsboro.

North Carolina's Highway Safety Program worked hand in hand with the Governor's Task Force on Drunk Driving, legislative committees and others in developing and implementing the Safe Roads Act of 1983. Approximately 1,600 chemical analysts were trained and certified during the period. Special courses were conducted for judges, district attorneys, law enforcement officials and others to orient them to the chemical test provisions of the new law. As the result of implementation of the new law, there has been a significant decrease in arrests for driving while impaired. However the use and abuse of alcohol continues to represent the most significant problem in highway safety. Although DWI arrests have decreased since implementation of the new law, this trend will certainly not be maintained without continuous efforts to keep the issue before the public.

Environmental health and sanitation issues continued to consume a major portion of our staff's efforts. Staff of the Solid and Hazardous Waste Management Branch inspected all seven hundred and thirty hazardous waste facilities to obtain compliance with North Carolina requirements. The Environmental Protection Agency has recently contracted with our agency to determine if there is a threat to the public health or the environment from five hundred and twenty old disposal sites that have been closed since November of 1980.

In response to an unusually large number of food poisoning outbreaks last year, special training sessions for sanitarians and food service personnel have been successful in emphasizing the need for better sanitation and foodhandling, particularly in feeding large gatherings of people. One area of continued concern is the increase of foodhandling activities in "supermarkets" (e.g., fresh squeezed orange juice, self-service salad bars, oysters in the shell, bulk foods, delis, etc.). A similar trend beginning with hot dogs, but leading to an unlimited menu, is occurring in convenience stores.

On the positive environmental side the "Temporary Opening" concept for shellfish growing waters has been expanded. This action, dependent upon the ability to detect transitory favorable climatic and bacteriologic conditions in marginal waters, has made many thousands of dollars' worth of shellfish available to the fishermen, yet without jeopardizing the health of the consumer. We continue, however, to face a proliferation of condominiums with on-site subsurface sewage systems in recreational areas. This, combined with marinas, etc., around sounds and estuaries, has greatly increased the potential for pollution of our shellfish waters.

In the area of dental health, 187 water systems serving 192 communities are now adjusting the fluoride content of their water supplies. Twenty-six additional towns are being served by naturally fluoridated water. In rural areas, one hundred thirty-five schools continue to provide fluoridated water for approximately 52,000 children. Over 383,000 children, grades K-8 in over 1,000 schools in 85 counties, participate in a weekly sodium fluoride mouth-rinse program. Eighty percent of these children reside in non-

From the Division of Health Services, Raleigh 27602-2091.

fluoridated areas of the State. Finally, over 58,000 children were referred by state and local staff to dentists in private practice for dental care. On-going evaluative studies have continued to show that these fluoridation and screening efforts are paying major dividends in the decrease of dental disease in our children.

The Human Tissue Donation Program has continued its efforts to provide information to the public through printed materials distributed by the driver licensing system, by participation in health fairs, and the presentation of programs to church, school and community groups, and through radio, newspaper, and television interviews. Almost 8,000 North Carolinians are signing Uniform Donor Cards each month and having their driver licenses show their willingness to be donors. Our information indicates that only one percent of persons who sign donor cards will actually die under circumstances that will allow for the recovery and transplantation of organs or tissues. Thus, there is need to greatly increase the pool of willing donors and to increase the number of community hospitals willing to participate in organ recovery activities.

Updated cervical screening guidelines were distributed to all local health departments and selected providers. The major change in these guidelines is that all women with two consecutive Class II Pap smears suggestive of significant cellular atypia are to be referred for evaluation and follow-up. Any Class III smear suggestive of dysplasia is also recommended for referral. We anticipate the revised guidelines to result in a fourfold increase in the number of women referred to rostered physicians in the private sector for the primary evaluation of abnormal Pap smears.

North Carolina's immunization program continues to be among the most successful in the nation. Thanks to collaborative efforts of our practicing physicians, school officials, both public and private, and our local health departments, more than 99% of North Carolina's children enter school having completed their full basic series. We have not had a North Carolina child contract measles for more than two years.

As a lead-in to my discussion of infant mortality I would like to summarize some of our efforts and concerns regarding services to women and children:

- The Crippled Children's Program provided diagnosis and treatment services to more than 20,000 chronically ill children with the cooperation and participation of more than 700 rostered physician specialists across the state.
- Our Developmental Evaluation Centers provided inter-disciplinary diagnostic service to 25,000 multi-handicapped children referred by private physicians and health departments.
- 96,000 low income pregnant women and babies in North Carolina are receiving physician prescribed protein supplementation via our hugely successful WIC Program.
- The Maternal and Child Health Branch supported prenatal clinics in 89 counties via the health department and in two additional counties via the local hospital. Approximately 15,000 indigent women were served by these clinics thanks in major part to the private practicing physicians who provide this care for next to no remuneration. In addition, almost 3,600 high-risk indigent women were served in special regional high-risk maternity clinics.

However, contrasting with these achievements we face some troubling challenges. Among them:

- New technologies, such as transplantation, bring the dilemma of remarkable health outcomes, but at startling costs. The Crippled Children's Program becomes a focus for this question of outcome versus costs — a topic of concern to the entire medical community. (One liver transplant versus how many strabismus corrections in children of low income families.) Is it any wonder that the field of medical ethics is burgeoning?
- Our Nutrition and Dietary Services Program is profoundly troubled and concerned with potentially dangerous and widespread food faddism and nutrition misinformation.

Let us turn now to a consideration of infant mortality in North Carolina. This health issue has received great attention and concern from individuals in health care and government at least since the early 1900s. In 1914, North Carolina's infant mortality rate was 90.3 deaths per 1,000 live births. This rate has thankfully declined over the decades. In 1970, our state's rate was 24.1 and in 1980 it was 14.1 showing a *rapid* decline of 41% over the decade.

However, our most recent rates have been 13.2 in 1981 and 13.7 in 1982. This represents a perplexing, though limited, increase in infant death in our state. It has occurred simultaneously with a period of unusual economic upset and, as such, has been the subject of much inquiry within our Division and elsewhere. In response to a request by the Governor, the State Center for Health Statistics, the Maternal and Child Care Section and a group of medical and health department leaders have made a detailed assessment of the recent increase in infant mortality. During the analysis, certain questions were raised and the answers developed as follows:

Is there a particular group of North Carolinians who appear to have experienced the greatest increase in mortality from 1981 to 1982?

Yes, certain subgroups of our citizens are affected, as follows:

- The increase in infant deaths from 1981 to 1982 occurred in *nonwhite* infants under 28 days of life (neonatal deaths). This nonwhite neonatal death increase was larger than would have been expected for the observed increase in nonwhite births and was clearly statistically significant.
- Detailed analysis of the numbers and rates for nonwhite neonatal deaths revealed increases among women who were
  - —ages 18 and above, with peak increases at ages 18 and 19;
  - —residents of urban areas, with peak increases in the biggest cities;
  - —delivered in our most capable medical centers, with peak increases at level III hospitals;

—of educational levels of twelfth grade or more.

- Of additional interest is that, while overall white neonatal mortality changed little, that finding concealed some increase in white neonatal deaths for mothers ages 20 to 24. All other white mothers enjoyed declines in neonatal deaths.

Did premature birth play a role in the nonwhite neonatal death increase?

Yes, prematurity did increase as follows:

- The percent of all nonwhite births with birthweights under 5½ pounds increased for nonwhite women from 11.8 in 1981 to 12.1 in 1982. In addition, the percent of all nonwhite births with birthweights under 3½ pounds increased from 2.4 in 1981 to 2.5 in 1982. This was especially true of extremely low weight infants in our big cities and our level III hospitals.
- In addition, there was an increase in neonatal deaths due to causes of death related to prematurity. Examples of these causes include extreme prematurity, hyaline membrane disease and multiple pregnancy.

Did birth defects play a role in the nonwhite neonatal death increase?

Yes, changes in deaths due to birth defects were as follows:

- There was an increase of 25 nonwhite deaths beyond expected due to birth defects. The largest proportion of these increases occurred in babies who were not premature to any great degree. No clustering in time or geographic location was evident in this group.
- Heart and blood vessel system abnormalities showed the most prominent increases.
- The increases in birth defects overall explained about as much excess mortality as the increase in deaths due to prematurity causes.

Did changes in the amount of prenatal care play a role in the nonwhite neonatal death increase?

Yes, as follows:

- While overall earliness and frequency of prenatal care improved for nonwhites, that improvement concealed some declines in the adequacy of prenatal care among mothers who experienced an extremely low weight birth. Thus, although the availability of prenatal care may not have declined to nonwhite mothers, the ability of our highest risk mothers to obtain it may have diminished.

From these findings, the group of medical and health care leaders recommended that further assessment be conducted through a collaborative review of individual medical records. In the meantime, private and public health care providers should:

- Continue to reach out to as many pregnant women as possible to assure early and frequent prenatal visits and to achieve high quality prenatal care for them.
- Enhance our efforts to prevent premature births through a multifaceted approach:
  —Prevention of unwanted pregnancy
  —Prevention of preterm delivery through high-risk identification and special health care as indicated for those at risk
  —Maintenance of high quality care of prematurely born infants, and
  —Provision of information to the public regarding the importance of prenatal care and the prevention of prematurity

Dealing with the issue of congenital malformations must await further studies. Consideration is being given to the establishment of a birth defects registry for North Carolina.

Progress and significant accomplishments thus vie with new challenges and problems — the agony and the ecstasy of Public Health. Your State Health Director of 1934 was acutely aware of both. In that year, the agony prevailed since Dr. James Parrott was stricken to his bed on the eve of his Conjoint Report after, as he put it, answering "the annual roll call thirty-seven years without a break." Nevertheless, Dr. Parrott, described by George Cooper as "sick, tired and weary, yet full of gratitude to his fellow physicians and hope for the future," penned the 1934 Conjoint Report from his sick bed and insisted that it be read in Pinehurst the following day. It contained the following words: "The philosophy of public health is the philosophy of the physician — it is the philosophy of sacrifice and service. The Health Department is the crowning glory of the medical profession. It is theirs, not by accident of discovery or the broad sword of gory conquest, but by the divine right of creation to be administered for the public good and for the public weal alone. It is the outstanding contribution of the physicians to the civilization of the commonwealth. I gain courage and take new hope when I am reminded that there are thousands of people alive today and enjoying life's richest blessings, and thousands of homes preserved that otherwise would have been destroyed were it not for the services which the public health department and doctors of North Carolina have rendered."

These words were spoken on May 2, 1934. They hold true on May 4, 1984. When officials from other states, with no little envy, sing the praises of North Carolina's public health system and its accomplishments, knowingly or not they laud its creator, nourisher and partner, the assembly of practicing physicians of this great state.



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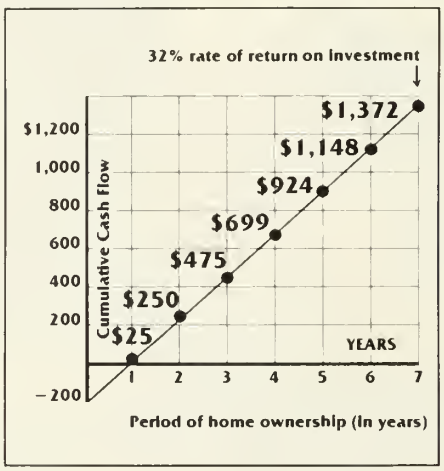
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Drug Therapy of Systemic Fungal Infections, Part II

Mark Gross, Pharm.D.

Miconazole (Monistat IV)

Another imidazole derivative for IV or topical use, miconazole has been used for a variety of systemic mycoses yet it is considered a second-line agent for systemic use despite frequent success when administered topically. This is because experience with the drug is limited even with many infectious disease consultants. Susceptible species include *Candida, Cryptococcus, Coccidioides immitis, Pseudoallescheria boydii,* and others.[3, 31] It is the drug of choice only for serious *P. boydii* infections. Like ketoconazole, miconazole is probably a fungistatic, suppressive agent that can effect a cure in disseminated mycoses only after long durations of treatment. However, it demonstrates more significant toxicities than ketoconazole. In the treatment of candidiasis, miconazole has been used with mixed results. Although thrush and esophagitis can be treated successfully, systemic candidiasis may be more resistant to the drug. Using miconazole in 37 neutropenic cancer patients, Jordan et al reported a 41% cure rate.[33] Successful outcome, however, was temporally associated with recovery of neutrophils, making it unclear whether cure was due to the drug, white cell function, or both. Duration of treatment ranged from 5-29 days with daily doses of 1.8-3 g/day. Fischer et al used IV miconazole in five children with chronic mucocutaneous candidiasis who were unresponsive to topical or oral antifungals (nystatin, flucytosine, amphotericin B, iodochlorhydroxyquin) or who required repeated courses of amphotericin B.[34] No complete cures were achieved in five subjects, long term follow-up was not reported, and other antifungals were used concurrently. This is in contrast to the superb results with ketoconazole in this group of patients.

Some investigators have suggested that miconazole may be useful as an alternative to amphotericin and flucytosine in cryptococcal infections.[35] Although successful outcomes were reported, none of the patients were cured when treated with miconazole alone and it had to be given intrathecally in several cases. Graybill has suggested that miconazole be used adjunctively with amphotericin B. However, there may be some evidence for antagonism.[36] Until further evidence indicates otherwise, miconazole should be reserved as a broad spectrum, second-line drug for patients who cannot tolerate standard antifungal regimens.

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References available from the NCMJ editorial office.

Miconazole is eliminated similar to ketoconazole, primarily via the feces in both metabolized and unchanged forms.[40] This highly protein-bound drug (90%) shows two-phase elimination after IV infusions with a terminal half-life of 24 hours, peak levels of 2-9 mcg/ml, and volume of distribution of 20 L/kg.[40, 41] CSF penetration is extremely poor and intrathecal administration is usually required to achieve therapeutic concentrations.[40] Each dose of miconazole should be diluted in 200 cc of D_5W administered over one hour, and sites should be changed frequently to avoid phlebitis.[3] Dosing is usually on a TID schedule. Dosages reported range from 200-3600 mg/day, depending on the mycosis, and duration ranges from one to twenty weeks (see table 1).[40] Reductions in dosing are not necessary for patients with renal disease. Competition between miconazole and other protein-bound drugs such as warfarin may potentiate their effects.[40]

Miconazole, like amphotericin B, may produce a severe anaphylactic response manifested by hypotension, arrhythmias, renal impairment, hyperkalemia, and metabolic acidosis after as little as 400 mg.[37] Therefore a test dose of no more than 200 mg should be given under the supervision of a physician.[38] Most of the adverse reactions associated with this drug are thought to be due to the castor oil vehicle in which miconazole was solubilized, "Cremaphor EL."[3] The vehicle can induce the release of histamine, resulting in severe pruritis unresponsive to antihistamines. It may also cause elevations in serum lipoproteins.[39] However, a new preparation has removed Cremaphor EL and replaced it with propylene glycol. No hepatic or renal toxicity has been associated with long-term use of miconazole, although transient elevations in liver enzymes are a rare occurrence.[3, 40]

Table 1
Range of Adult Doses of Miconazole

Organism	Dosage range (mg/d)	Duration of Successful tx (weeks)
Coccidioidomycosis	1800-3600	3 to more than 20
Cryptococcus	1200-2400	3 to more than 12
Candidiasis	600-1800	1 to more than 20
Paracocci.	200-1200	2 to more than 16
Dosing in children — 20-40mg/kg/d		

(source: ref. 39)

Flucytosine (Ancobon)

Flucytosine is an antifungal that may be used alone or in combination with amphotericin B for some systemic mycoses. Unfortunately its use has been limited by the tendency of many species to develop resistance. Flucytosine (5-FC) functions by being selectively converted into 5-fluorouracil within the fungal cell and, except in concentrations greater than 100 mcg/ml, not in mammalian cells.[42] The drug is active against *Candida* species, *Torulopsis*, *Cryptococcus*, and chromomycosis.[43] The site of action is thought to be at both DNA and RNA synthetic pathways.[44]

5-FC is best known for its use in cryptococcal meningitis, either alone or in conjunction with amphotericin B. Although it has been shown to be curative as a single agent for cryptococcal meningitis, combination therapy is probably superior because of the shorter interval of treatment required and the greater efficacy against 5-FC resistant organisms.[16, 42] The incidence of 5-FC resistance may be 1-2% for cryptococcal species, as high as 50% for candidal species.[45] Since secondary resistance can develop during therapy, a conservative strategy would avoid the singular use of 5-FC for any mycosis. However, normally resistant pathogens may be susceptible in the bladder because of very high urinary concentrations and therefore 5-FC may be used alone for urinary candidiasis if one realizes potential problems. Amphotericin B and 5-FC have also been used empirically in aspergillus infections despite the lack of clinical studies confirming any clinical advantage to this combination.[3] Despite a scarcity of clinical data, 5-FC and amphotericin B may be used together for candidal infections. The two drugs have been found to have a slightly additive effect *in vivo* and *in vitro*.[46]

5-FC is 78-89% absorbed after oral administration. Normal subjects demonstrate an excretion half-life of 4.2 hours, and the drug is 90% excreted in the urine.[47] Following hemodialysis 20 mg/kg should be given to maintain steady state levels.[42] Patients with renal disease should receive reduced doses based on their creatinine clearance (see table 2). Ideal therapeutic levels lie between 50 and 100 mcg/ml, achievable with doses of 150 mg/kg/day in patients with normal renal function. CSF levels are 71-85% of serum levels following oral dosing.[47]

Most patients tolerate 5-FC without serious adverse

Table 2
Flucytosine Dosing in Renal Failure

Creatinine Clearance ml/min/1.73m^2	Dose mg/kg/day
Greater than 40	150
20-40	75
10-20	37.5
less than 10	measure serum drug levels

(source: ref. 2)

Table 3
Antifungal Therapies

	Uses	Regimen	Toxicity	Comments
Amphotericin B	Systemic Candidiasis Cryptococcosis (with 5-FC) Coccidioidomycosis Histoplasmosis Aspergilosis	1 mg IV test dose then 10 mg IV to 1 mg/kg/day maximum dose Increase by 5-10 mg/day	Nephrotoxicity Anemia Hypokalemia Hypomagnesemia Thrombocytopenia Immediate reactions: Anaphylaxis Shaking chills, Fevers	Avoid preparing in saline solutions Monitor: electrolytes, S_{cr}, Hgb, Hct, platelets.
Flucytosine (5-FC)	Fungal Urinary Tract Infections Candidiasis* Cryptococcosis Aspergilosis* Chromomycosis	100-150 mg/kg/day PO, q6h adjust dose in renal failure (see table 2)	Nausea, Vomiting, Leucopenia, Thrombocytopenia, GI irritation, Hepatic dysfunction	Serum levels greater than 100 mcg/ml associated with toxicity and systemic 5-FU effects.
Ketoconazole	Candidiasis† Cryptococcosis† Histoplasmosis† Blastomycosis† Chromomycosis†	200-600 mg/day PO (qd or bid) larger doses for severe infections	Hepatic dysfunction Nausea, vomiting, diarrhea, gynecomastia suppressed cortisol and testosterone levels	Avoid concomitant use of antacids or other anti-ulcer drugs. Best absorbed in acid stomach or with food.
Miconazole	*Pseudoallescheria* (Petriellidium) *boydii* Candidiasis‡ Cryptococcosis	200-3600 mg/day 200 mg test dose (see table 1)	"Cremaphor EL" vehicle: hyperlipidemia, anaphylaxis, pruritis, arrhythmias rare elevated liver function tests	Re-formulated vehicle may eliminate toxicities during administration.

* Used in combination with Amphotericin B with questionable efficacy
† For non-life threatening infections in patients with intact immune functions.
‡ Second-line therapy when Amphotericin B cannot be used.

effects, even in long dosing periods but its side effects can be serious. Most adverse effects involve irritation to the gastrointestinal tract, nausea, vomiting, and diarrhea.[42] Intestinal perforation is a rare complication.[43] Levels that consistently exceed 100 mcg/ml are associated with myelosuppression, pancytopenia, and hepatotoxicity possibly due to conversion to 5-fluorouracil in mammalian cells, and therefore such elevated levels should be avoided. 5-FC toxicity remains a problem in treating seriously ill patients and those with reduced renal function.

Amphotericin B Methyl Ester

Amphotericin B methyl ester was synthesized in an attempt to create a congener of amphotericin B which maintains its antifungal potency but lacks its nephrotoxicity. Early studies showed that amphotericin B methyl ester retained the anti-fungal activity of amphotericin B but nephrotoxicity was uncommon even at doses five times the normal amphotericin B concentration.[48] A recent study showed that severe neurological damage characterized by diffuse white matter degeneration occurred in human subjects, often leaving them with profound deficits.[49] It was theorized that impurities in amphotericin B methyl ester were responsible for this toxicity but this was disproven when similar reactions occurred with lots that were either 35% or 65% pure.[49] Leukoencephalopathy of the methyl ester compounds remains a concern and has delayed their development in clinical practice.

Conclusions

If used rationally, antifungal agents can effectively eradicate systemic fungal infections with a minimum of adverse reactions or toxicities (see table 3). Depending on the patient, a highly toxic fungicidal drug such as amphotericin B may not always be needed. If the patient is immunocompetent, adequately compliant, and has a pathogen which is susceptible to an oral agent such as ketoconazole, there is substantial evidence that prolonged (six months or more) suppressive therapy with this agent may be as effective as a course of intravenous therapy with amphotericin B so that significant toxicities may be avoided.[5, 7, 8] Conversely, an immunosuppressed patient with a life-threatening mycosis such as endocarditis or meningitis will need fungicidal therapy with one or two drugs, and severe toxicities may be inevitable. Despite recent advances in antifungal therapies, the chances of complete eradication of systemic fungal infections in an immunocompromised host remain poor since the immune system of the host plays such an important part in the development of disease. We have yet to consistently intervene successfully in this aspect of the host-parasite confrontation.

St. Ronald's Ballet — Strychnine Poisoning

Ronald B. Mack, M.D.

[This treatise is not meant to be either sacred or profane. I am apologizing at the outset.]

MANY academic physicians allege that they eschew eponyms (repeat this rapidly six times), but I love them. In the June 1984 issue of the *Journal of Pediatrics* in the Letter to the Editor section, there is again a request to limit the use of eponyms.[1] Having a disease named after a person or persons seems perfectly delightful to me; it is so romantic, so heroic, so laudatory. I really believe that no one will ever name a disease after me so I decided to name one after myself — St. Ronald's Ballet. After you read this article, see if you don't agree.

I would guess that the naming of diseases for saints began during the period of medieval medicine which covers the period between 500 AD and 1500 AD.[2] Apparently in the Middle Ages the physicians of the time had to try to combine the pagan medical traditions of the invading barbarians with the classical traditions of the now destroyed Roman Empire and the Christian religion.

Medieval medicine is divided into two periods: the early period known as the era of *monastic medicine* and the late period referred to as the period of *scholastic medicine*. In the monastic period, as the name implies, monks played a major role in the providing of medical care and in the composition of medical texts (the printing press after all would not be available until 1448 when Johann Gutenberg put it together and the photocopy process did not occur until our historical period). In this early medieval period, the Church, allegedly, emphasized interest in the soul as opposed to maladies of the body. Christianity, early on, apparently had its own theory of disease: either disease was punishment for sins, or possession by the devil (I still believe this but don't tell anybody, please!!), or the result of witchcraft. Therefore, their treatment consisted of prayer, penitence and the assistance of saints. The Council of Clermont in 1130 forbade monks to practice medicine and this job now became the province of the secular clergy, i.e., the non-monastic priests. Scholastic medieval medicine which occurred in the second half of the Middle Ages was merely a repetition of the Greek Medicine period (500 BC to 500 AD) and its theories, plus many elements of supernaturalism including the invocation of numerous saints specializing in specific diseases. My colleague, Dr. Robert W. Prichard of Bowman Gray School of Medicine — an esteemed medical historian as well as an esteemed pathologist — suggests that another element in the naming of some diseases after saints is that some of the requirements of sainthood mandated the performance of miracles which certainly could have been observed to occur in a medical context in many instances.

The list of diseases named for saints is quite long indeed. The best known to most of us is St. Vitus Dance AKA Syndenham's Chorea (two separate eponyms). Chorea is such a peculiar phenomenon that in the Middle Ages it was also known as St. Anthony's dance, St. Guy's dance, St. Modestus' dance and originally St. John's dance. The term dance in these eponyms seems to be related to the *dancing mania*, a really unusual psychic aberration which caused epidemics whereby literally thousands of men and women danced till they collapsed from physical exhaustion (today they are called "break dancers"). St. Anthony was really very lucky, he had three diseases named for him: chorea (St. Anthony's dance), erysipelas (St. Anthony's fire) and ergotism (also St. Anthony's fire). Hemorrhoids, known as St. Fiacre's disease, should properly be called St. Anthony's fire as well — at least in my opinion.

In the name of St. Sebastian (the plague) where is all this leading to? My real subject today is *strychnine* poisoning. We recently had a young adult patient who was given some strychnine (without requesting it) in his regular supply of cocaine. He entered our emergency room with "convulsions." My interest was piqued because this poison is a fascinating and old enemy. Strychnine is an alkaloid extracted from the seeds of the Strychnos nux-vomica tree and has been used since the 16th century to kill rodents and also used in medical therapy although it has no known therapeutic value. This substance, a white, bitter-tasting, crystalline, odorless, colorless alkaloid, is available in dozens of products, even as we speak — primarily rodenticides but also veterinary products, and laxatives, tonics, or stimulants for human use and of course an adulterant of illicit drugs of abuse. One of my colleagues remarked that in the spring, when he was a young lad, he was given nux-vomica as a tonic.

The pharmacokinetics of strychnine are fairly well defined. Absorption of strychnine occurs quite rapidly from the GI tract as well as the nasal mucosa (the latter makes it especially inviting for those who adulterate cocaine). Furthermore, it is rapidly absorbed from subcutaneous or IM injection. This drug is apparently not bound to protein to any important degree and thus rapidly enters the brain and cord, liver and kidneys. Most of the strychnine is metabolized by microsomal enzymes in the liver. Within minutes after an ingested dose strychnine can be detected in the urine. By St. Giles (leprosy) and St. Hubert (rabies),

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strychnine is a weird toxin. Apparently this drug produces its clinical effects by competitively blocking the postsynaptic receptor sites for the inhibitory transmitter *glycine*. Now glycine is the big deal here as it is thought to be the primary inhibitory transmitter in the spinal cord and to a lesser extent in the brain stem. Glycine is sort of like my Dad's cousin Charlie; during Prohibition his job was to keep the operation quiet and running smoothly. If Charlie was neutralized all hell broke loose. When an overdose of strychnine is taken in concentrations high enough to compete with glycine, the inhibition of motor neuron acitvity is decreased and forceful muscle contractions occur. Although this toxin excites all parts of the CNS the important scenario from the clinician's point of view is its effect on the spinal cord motor neurons especially at the postsynaptic receptor sites of the ventral horn motor neurons.

The lethal dose of strychnine in human beings is estimated to be about 15-30 mg, but deaths have been reported from much less. The onset of symptoms occurs quite rapidly, usually within 15-30 minutes after ingestion, and relate entirely to the blockage of the glycine receptors as has been stated. (You know, that is so true. As a teenager I remember my mother telling me not to inhibit my glycine.) Early on, the patient experiences a feeling of restlessness and anxiety with a heightened sensory awareness of sight and sound, not to mention muscle tightness. If a physical exam is performed at this time you might notice hyperreflexia and twitching of small muscle groups. With larger doses there is rapid progression to the so-called strychnine "convulsions" which are indeed horrific. These convulsions consist of generalized symmetrical tonic extensor muscle spasms with opisthotonus (hence, St. Ronald's Ballet). The very powerful dramatic extensor spasms are produced by the specific blockade of reciprocal inhibition among antagonistic muscle groups (I knew it all the time!!) and are really quite dissimilar to the classic tonic-clonic seizures arising from a seizure focus in the cerebral cortex. Lethal asphyxia can occur secondary to intense spasm of the thoracic and abdominal muscles and, of course, the diaphragm. The weird part of this clinical picture is the fact that even minimal sensory stimuli may set off violent muscle contractions lasting 30-120 seconds or more [For St. Martin's (alcoholism) and St. Zachary's (mutism) sake, don't even sneeze in the patient's presence.]. The "convulsions," trismus, risus sardonicus and opisthotonus in a conscious patient makes this clinical picture an unforgettable event for all concerned. The miserable patient can experience these abnormal clinical features from 2 hours to 2 or 3 days and (with adequate oxygenation) remains conscious. Between the "attacks" complete muscular relaxation occurs for 5 to 15 minutes or more but another attack ensues from any external sensory stimulus when the hyperexcitable state returns. When death occurs it does so within 1 to 3 hours after the strychnine enters the body; survival is very good (usually without important sequellae) if the patient "makes it" beyond the first 5 to 6 hours.

As you probably can imagine, there are multiple complications as a result of the violent repetitive muscle contractions; prominent adverse clinical features must therefore include *rhabdomyolysis* and subsequent myoglobinuria, *lactic acidosis* with markedly elevated lactate levels, and unbelievably depressed arterial pH levels and *hyperthermia*. The rhabdomyolysis occurs as a result of the muscle cell injury and causes elevated levels of muscle enzymes, e.g., CPK, LDH, SGOT. The myoglobinuria that forms as a result of this muscle injury can and does lead to renal failure. Lactic acidosis is probably the most common cause of metabolic acidosis that you will run into in an Emergency Room and quite readily occurs with seizures that are of cortical or noncortical etiology as well as with maximal exercise. The remarkable muscle activity that occurs in strychnine poisoning causes heat production to proceed at a rate faster than the heat loss and hyperthermia is the result.

Well, by St. Ignatius (pellagra) and St. Appolonia (toothache) how do you diagnose and treat such an awesome encounter of the toxic kind? The history and physical remain the best diagnostic tools available. You must consider strychnine poisoning in any unfortunate patient who retains consciousness during what appears to be violent convulsions. You can detect strychnine via thin layer or paper chromatography but these determinations will most likely not help you at the bedside. The management of a patient intoxicated by strychnine obviously mandates suppression of the convulsions, support of the cardiorespiratory system and correction of the acid-base imbalance. It would be wonderful if administering *glycine* would suppress the convulsions but so far this chemical has not been very useful at the bedside. The method of choice in the control of the seizures has not yet been written in stone but many authorities recommend using intravenous diazepam initially. This benzodiazepine is felt to be a noncompetitive antagonist to strychnine. If diazepam fails to quell this disaster, even with large doses, then cerebral anesthesia using barbiturates should be considered; some authors would also add pancuronium to this regimen, to produce muscle paralysis. You may need to combat the lactic acidosis with sodium bicarbonate, but the biochemical abnormality can improve rapidly with cessation of muscle spasm activity and ventilatory support. Rhabdomyolysis may not lead to precipitation of myoglobin in some patients if the urine is rendered alkaline. Hyperthermia should resolve with elimination of muscle spasms plus the use of cooling blankets and/or iced saline gastric lavage. Fluid diuresis or dialysis do not seem to be of value in this poisoning and should not be used.

Why St. Ronald's Ballet you ask, why not St. Ronald's Dance? Well, you must believe I asked but the Dance was already taken. With your permission I would like to name a condition after my grandson, St. Jeb (carrying a stuffed animal to the awarding of your Nobel prize).

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Goosey Patients: Relationship to Jumping Frenchmen, Myriachit, Latah and Tic Convulsif

E. Wayne Massey, M.D.

• *Goosey patients are unusual, but not rare. Similar conditions have been described in other cultures for centuries.*

"GOOSEY people are not rare and we should all think twice before goosing someone."[1] Patients with exaggerated startle response have been emphasized for many years, in fact for centuries.

Latah in Malaysia, Piblokto in the Arctic, and Amok in Malaysia all involve reflex responses and have been known for centuries.[2] Myriachit, described in Siberia before the 1880s, the jumping Frenchmen of Maine in the 1880s, and Tic Convulsif in the 1880s also involve involuntary movements of jerking, jumping or startle.

In 1980, J. E. Hardison[1] reported several patients from the southern United States who had a startle response and who had been called "goosey." Goosey is defined as "susceptible to or reacting strongly."

A startle response is an uncontrolled jerk or jumping motion in response to an unexpected strike. It may be a form of myoclonus which is involuntary shock-like contractions of one or more muscles which may be restricted or occur multifocally throughout the body or even displace the entire body. Myoclonus often follows a repetitive pattern and is usually irregular, although sometimes there is a rhythm. Jumping, startle and goosey seem to be similar. They cannot be self-induced.

Dr. Hardison referred to his experience at age 17 when his girlfriend confided to him that her mother was goosey. In addition, his father had told him of two goosey boys in a small town in North Carolina where his father was raised. He referred to another case from Tennessee and mentioned several cases seen by his fellow physicians over the years.[1]

Present Cases

Two brothers seen at Duke Hospital, age 23 and 27, have manifested jumping or startling in response to minimal stimuli. Both patients had experienced this from childhood and were born and raised in the southwestern part of North Carolina. Although adults when examined, both stated that they had been goosey since early childhood. They demonstrated a marked or violent jump in response to sudden noise or being startled. These did not occur spontaneously and there was no loss of consciousness. Both patients had a normal neurological examination. Neither manifested coprolalia but both had experienced echolalia on occasion. These patients had been termed goosey by their friends and relatives and fit the pattern described in other North Carolina patients.[3]

Discussion

This syndrome seems to be related to other forms of startling that have been described. These include the syndrome of Jumping Frenchmen of Maine, emphasized by Beard in 1880, of Myriachit, described by Hammond in 1884, of Latah, described in the Malayan literature as early as the 14th century, and similar to Tic Convulsif as de-

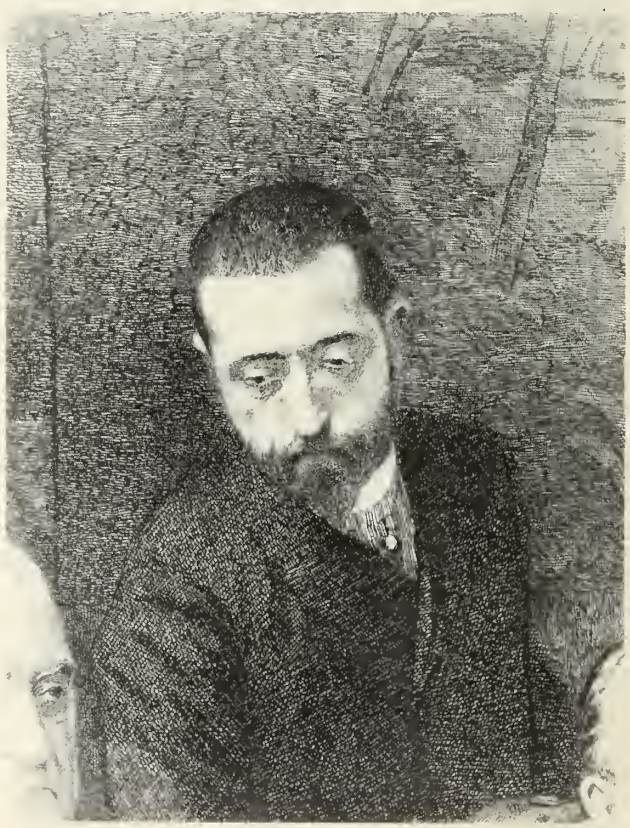


Figure 1. *Dr. G. Gilles de la Tourette. Photo from the National Library of Medicine.*

From the Division of Neurology, Duke University Medical Center, Durham 27710



Figure 2. *Dr. George M. Beard. Photo from the National Library of Medicine.*



Figure 3. *Dr. William A. Hammond. Photo from the National Library of Medicine.*

scribed by Gilles de la Tourette in 1884 (figure 1). Echolalia, repetition of words just spoken, or coprolalia, uncontrollable use of obscene language, may occur in these disorders which begin in childhood, affect both men and women, and may be hereditary (see table 1).

In 1880 at the Sixth Annual Meeting of the American Neurological Association, Dr. George Beard (figure 2) presented a paper on "Experiments with the Jumpers or Jumping Frenchmen of Maine,"[4] describing subjects of French Canadian extraction, "mostly lumberjacks," who could not restrain from jerking or jumping in response to a sudden strike or kick. They lived in the Moosehead Lake region of Maine.[5] When two "jumpers" were close together they struck each other simultaneously with severe blows associated with startle. Some of the patients had echolalia and some responded automatically to a loud command by repeating the command and executing the order even though it may have been dangerous or humiliating to them.

Dr. William Hammond (figure 3) described Myriachit in 1884[6] with an epidemic of "jumpers" in Siberia (myriachit means "to act foolishly"); it had been described earlier in the foreign literature.[7] Echolalia and echopraxia, pathological repetition of the acts of other people, sometimes occurred in an automatically obeyed command.

Table 1
Comparison of Jumping Frenchmen, Myriachit, Latah, Goosey, Tic Convulsif

Syndrome	Jumping	Latah	Myriachit	Goosey	Tic Convulsif
Year reported	1880	1500's	1884	1980	1825
Sex	M	F	M, F	M, F	M, F
Onset	Child	Adult	Epidemic	Child	Child
Familial	+	?	+	+	?
Geography	Frenchmen	East; Africa	Siberia	Southern U.S.A.	Universal
Neurological findings	0	0	+	0	+
Length of attack	Seconds	Seconds — Hours	Hours	Seconds	Seconds
Imitate	+	0	0	0	0
Startle	+	+	+	+	0 (Spontaneous)
Echolalia/coprolalia	+/−	+/+	+/−	+/−	+/+

The movements are similar in each; resolution is the same; loss of consciousness does not occur in any.

Latah has occurred in women in primitive societies for centuries; they manifested immediate and accurate repetition of a noise, music or gesture, often associated with coprolalia.[8] Both these entities may be hereditary and the etiology is unknown.

The older neurological literature assumes the similarity of jumping to Tic Convulsif of Gilles de la Tourette syndrome.[9] Although this lifelong syndrome begins in childhood, it produces spontaneous movements that are not triggered by startle but are associated with coprolalia.[2] However, it is unlikely that these entities are related.[3]

Dr. Harold Stevens[3] has reported two additional cases of "jumpers" in 1965. His second patient was a 52-year-old woman who had a niece with a similar affliction. Both were of Protestant-Scotch-Irish-German extraction and were reared in North Carolina.

Startle responses are unusual but certainly not rare. They occur in various cultures and possibly are similar (despite the varied labels) although not identical in clinical characteristics. Goosey, in North Carolina, seems to be similar to startle responses described in our culture. Startle cannot be self-induced. It can be suppressed in many people, however, when they are properly warned.

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Down the Wrong Garden Path

Ronald B. Easley, M.D., Ph.D.

• *Expecting all four cardinal features of Parkinsonism before suspecting the presence of Parkinson's disease can lead down the wrong garden path.*

THERE are four cardinal features that come to mind when I am considering a diagnosis of Parkinsonism: 4 cps tremor at rest, muscular rigidity and mask-like facies, bradykinesia with a flexed and shuffling gait, and postural instability. Intellect, power, cranial nerve function and sensation are unaltered (table 1). I have been down the wrong garden path on two occasions during the past year for expecting all of the above features before suspecting the presence of Parkinson's disease. The following case report will illustrate this basic misconception.

E.K. is a 66-year-old woman who had been gainfully employed until retirement at age 65. She appeared on three occasions to the emergency department with symptoms suggestive of acute panic episodes. A serum thyroxine level obtained on her last ED visit was 12.2 mcg/dl. On examination she appeared fearful with a resting tachycardia, fine intention tremor of the outstretched hands, and hesitant speech. She had a stooped posture and expressionless facial appearance. There was a history of recent insomnia and loss of appetite. She had a slow but stable gait, and rapid alternating maneuvers were poorly performed. A TRH stimulation test elicited a normal TSH response.

She became uncooperative and demanding at home and her family decided to place her in a convalescent center. Her mobility continued to deteriorate to wheelchair confinement. She was accused of faking her disability by family as well as nursing assistants. Examination two months later disclosed muscular rigidity, hypomimia and decreased blink frequency, fine intention tremor and hesitant speech. The proverbial bolt of lightning finally struck and she was placed on Carbidopa. Bradykinesis and muscular rigidity dissipated and she is now living independently.

Rest tremor is typically the first symptom of Parkinson's disease. Perhaps 20-30% of patients, however, will not develop the rest tremor until late in the disease.[1] In 1817 James Parkinson stated "so slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens that the patient can form any recollection of the precise period of its commencement."[2]

Slowness of movement and expressionless facial appearance are often interpreted as concomitants of depression.

TABLE 1
Signs of Parkinsonism

Typical Features
4cps tremor at rest
Muscular rigidity (cogwheel)
Slowness of movement
Postural instability
Mask-like facies
Less Typical Features
8-12cps action tremor
Distal dystonic movements
Impaired upward gaze
Hesitant speech
Slowness of chewing and swallowing
Preserved Functions
Power
Intellect
Cranial nerve function
Sensation

Yet a depressed person can be forced into rapid movement; the Parkinsonian will stumble or fall. And don't be misled by the presence of an action tremor; 10-20% of Parkinsonians will have this when asked to posture.

Parkinson's disease results from a deficiency of dopamine in the caudate and putamen (striatum). The pathologic hallmark is cytoplasmic inclusion bodies (lewy bodies) in the pigmented neurons of the substantia nigra. Dopamine regulates intracellular cyclic AMP in the striatal neurons. These events modify input into the pallidum, ventral lateral thalamus, and subsequently the motor cortex. It is still debated whether treatment of Parkinson's disease alters its mortality rate. Some studies demonstrate an incidence of dementia when high dose Levodopa is used.[3] Perhaps the addition of a dopa decarboxylase inhibitor has reduced this complication. The improvement in the quality of life with treatment remains undebatable.

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From the Piedmont Diagnostic Clinic, 6005 Russell Road, Durham 27712.

Thyroid Malignancy Masquerading as Thyroiditis

Warner M. Burch, M.D.

• *Two cases of thyroid cancer that appeared at first to be thyroiditis.*

I RECENTLY cared for two patients who taught me that thyroid cancer may masquerade as thyroiditis. Both patients were initially thought to have thyroiditis in that each had a sudden onset of thyroid enlargement and a low radionuclide thyroidal uptake. What was unusual about these patients was that their clinical course was atypical for a benign self-limiting process and led to further investigations.

Case Presentations

Patient 1

A 16-year-old girl noticed swelling in her anterior neck, anxiousness, and inability to sleep one month after an upper respiratory infection. She denied any fever, palpitations, weight loss, neck pain, or unusual exposure to X-ir-radiation. Her maternal grandmother had a goiter. On physical examination, the pulse was 140; the left lobe of the thyroid was smooth, non-tender, and measured 4 cm in width and 5 cm in height; the right lobe and isthmus were just palpable but not enlarged. No other abnormalities were noted.

Serum thyroxine was 13 μg/dl (normal 5-12); T_3U, 54% (normal 34-45); and thyroidal uptake of technetium-99m pertechnetate was low without any focal abnormality. Her physician referred her to me. Two weeks later, she appeared to be euthyroid and her serum thyroxine was 6.3 μg/dl; T_3U, 46%; and 24-hr thyroidal I-131 uptake 1%, a value too low for accurate scanning. The sedimentation rate was 10 mm/hr; thyroid microsomal and thyroglobulin antibodies were negative. All of these findings were consistent with painless thyroiditis (it is relative common to see transient hyperthyroidism in this entity). I prescribed aspirin 600 mg qid and her symptoms abated over the next few weeks.

The enlarged left lobe did not regress over the next ten months. This worried me since the gland should have spontaneously decreased in size over this interval if painless thyroiditis was the cause. Other benign enlargement such as focal Hashimoto's thyroiditis seemed less likely with absence of thyroid microsomal antibodies. I performed fine needle aspiration biopsy of the thyroid.[1] The aspirate revealed changes consistent with papillary thyroid carcinoma. There were varying size nuclei, increased gran-

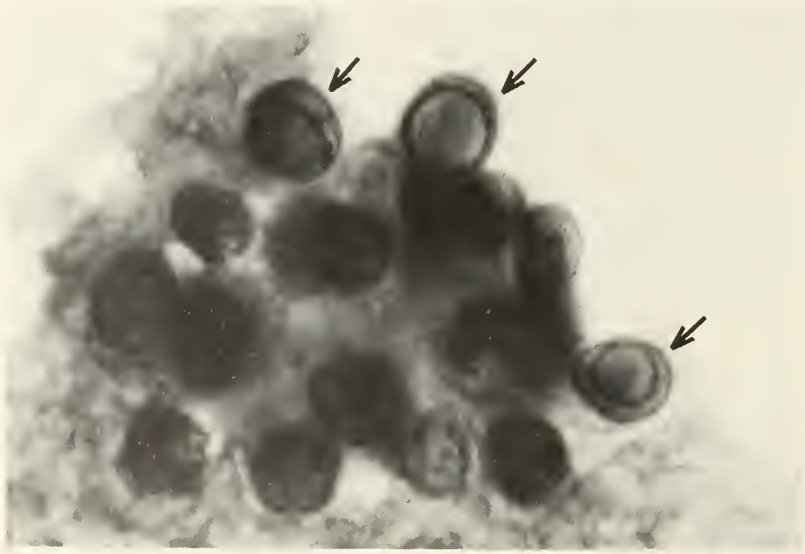


Figure 1. *Photomicrograph of fine needle thyroid aspirate from Patient 1. The arrows mark three Orphan Annie cells. The appearance is due to large round inclusions that are actually an invagination of the cell membrane. Finding these cells strongly suggests thyroid carcinoma.*

From the Department of Medicine, Duke University Medical Center, Durham 27710.

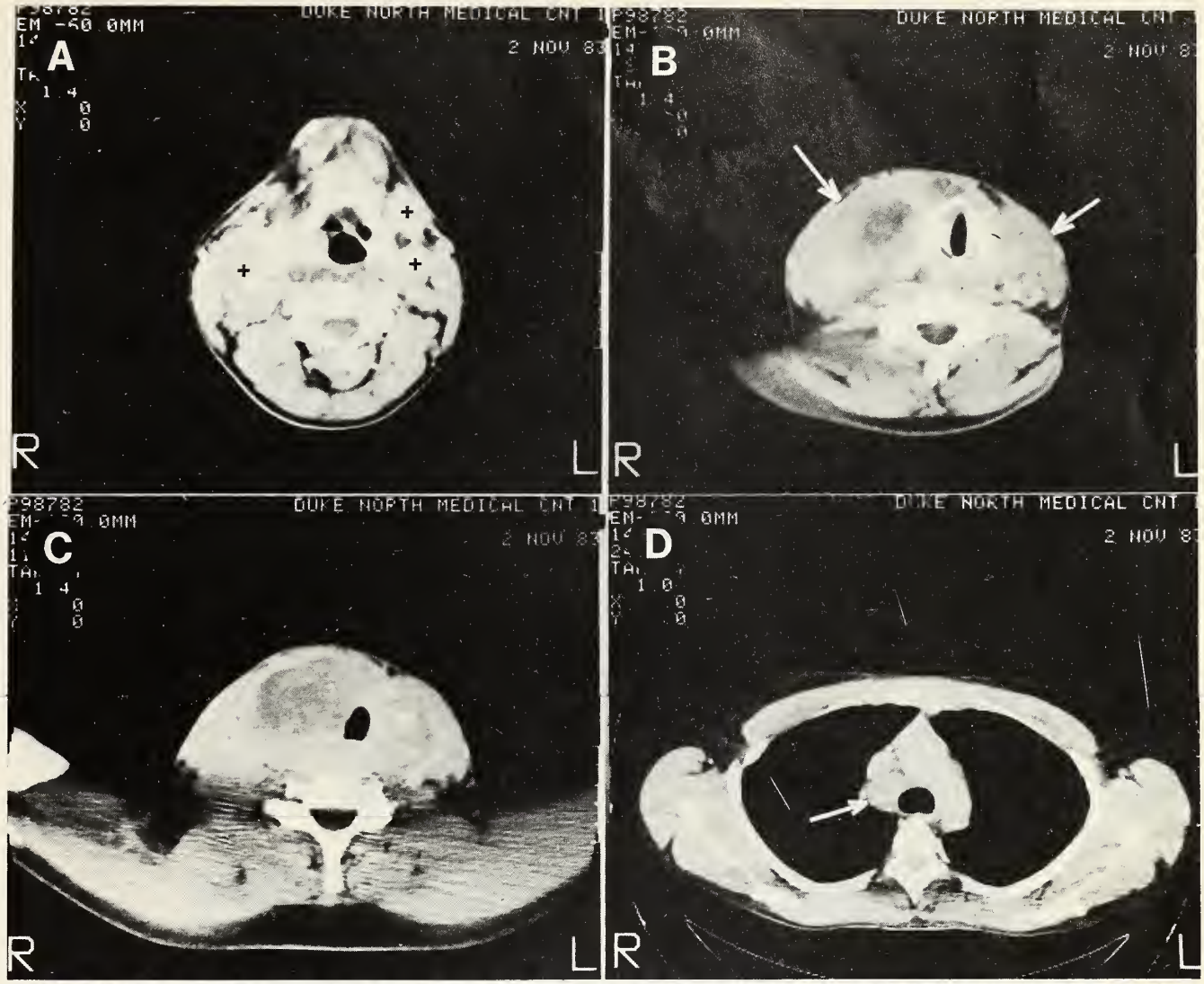


Figure 2. *Computerized tomographic scan of the neck and upper thorax of Patient 2. The sequence begins in the upper neck just inferior to the mandible* (A), *progresses inferiorly to the level of the larynx (B), then to the thyroid below the larynx (C), and finally to the level of the carina in the chest* (D). (A) *Note large masses (marked with +), presumably lymph nodes.* (B) *The arrows point to the thyroid lobes, which are greatly enlarged. The right lobe contains a hypodense area and displaces the larynx to the left.* (C) *The massive increase in thyroid size including isthmus has compromised the tracheal aperture.* (D) *The mass (marked with arrow) extends down the trachea to the level of the carina.*

ularity of nuclear chromatin, and cells with a washed-out nuclear appearance — so called Orphan Annie cells (see figure 1). These cells are often found in aspirates of papillary thyroid carcinoma and though not diagnostic are suggestive of thyroid cancer. At surgery, papillary thyroid carcinoma involved the entire left lobe and several regional lymph nodes contained tumor. Treatment consisted of total thyroidectomy, postoperative thyroidal ablation with radioactive iodine, and thyroid replacement. Two years following surgery, she remains healthy and the total body I-131 scan continues to be negative.

Patient 2

A 27-year-old man presented to his physician with sudden onset of pain and enlargement of the right side of the neck for two weeks. He had no other symptoms or prior history of X-irradiation to the head or neck. His father, paternal aunt, and paternal grandmother had goiters. There was a 3 cm by 4 cm nodule in the right lobe of the thyroid which was slightly tender. The left lobe was palpable and questionably enlarged. The serum thyroxine was 7.7 μg/dl; sedimentation rate, 20 mm/hr; 24-hr thyroidal I-131 uptake, 4% (normal 10-30%); and the thyroid scan demonstrated diffuse decreased uptake throughout the gland. Aspirin was prescribed for subacute thyroiditis. The patient did not seek follow-up until four months later when he presented for shortness of breath that he noted while working strenuously as a farmer. He was referred to me for treatment. He had noticed progressive enlargement of the anterior neck without pain or weight loss. On physical examination, the thyroid measured 20 cm in total width with each lobe being 12 cm in height. The goiter was firm,

smooth, bosselated and extended from the angle of the mandible to the sternal notch. The serum thyroxine was 8.4 μg/dl and thyroid microsomal antibodies were negative. Fine needle aspiration biopsy identified no elements of normal thyroid tissue. The majority of cells were uniform and had scant cytoplasm. The cytological findings were compatible with chronic lymphocytic thyroiditis or undifferentiated carcinoma. Computerized tomography demonstrated multiple masses within the neck and a mediastinal soft tissue density that extended down to the carina (figure 2). At surgery, a malignant teratoma of the thyroid was found but could be only partially removed. This is a rare tumor of the thyroid which occurs most often in children and has a dismal prognosis in adults — most patients die within 10 months of diagnosis.[2] This patient was not an exception; despite radiation therapy, his disease progressed with pulmonary metastasis and death within two months of surgery.

Discussion

Each of these patients was presumed to have thyroiditis (recent and relatively sudden onset of thyroid enlargement associated with low radionuclide thyroid uptake and diffuse imaging intensity), the first having painless thyroiditis and transient hyperthyroidism and the second, subacute thyroiditis. However, nodularity that persists longer than anticipated for a benign inflammatory condition (patient 1) or increases in size (patient 2) warrants further studies. Fine needle aspiration biopsy is safe, easy to perform,[1] and accurate,[3] but requires expertise in cytological interpretation. Both patients had underlying malignancy accompanying or mimicking thyroiditis. Such cases of "pseudothyroiditis" are most likely due to thyroid carcinoma but other malignancies such as parathyroid carcinoma have mistakenly been diagnosed as thyroiditis as well.[4] Other benign conditions such as hemorrhage into a cyst or into an adenoma can also be confused with thyroiditis. In such cases of "thyroiditis," fine needle aspiration thyroid biopsy leads to the correct diagnosis, excludes malignancy, and avoids prolonged delay in treatment.

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Growing Pains

Jonathan J. Berry, M.D.

• *Severe osteoarthritis may be the clue to acromegaly.*



Figure 1. *Pictures of patient, D. B., at ages 12(A), 40s(B), 50s(C) and 70s(D, E) showing the development of acromegalic features over time.*

ONE of the classic problems in outpatient medicine is looking at a simple problem and not seeing the broad picture. D.B. was a case in point. Her visit was scheduled at the end of the day in my clinic and she complained of the mundane problem of sore joints. My first thought was that she was just another 73-year-old woman with degenerative joint disease and that Indocin or Motrin would solve the problem. Everything else on her physical examination was normal except that she fit into that broad category of unusual-looking adults. Just in case, however, I performed the routine laboratory tests including rheumatoid factor, sedimentation rate, electrolytes, hemogram, thyroid panel (all normal), as well as getting hand, hip and knee films. She was scheduled for orthopedic consultation. Not too long after this I received a call from an orthopedic resident telling me about the films ("osteoarthritis") and mentioning parenthetically that "Yes, she does look out of the ordinary. Her face and features are in general larger than ordinary, and has anybody thought of acromegaly?" Now, I thought, what are the chances that a 73-year-old undi-

From Box 31187 Duke Hospital, Durham 27710.

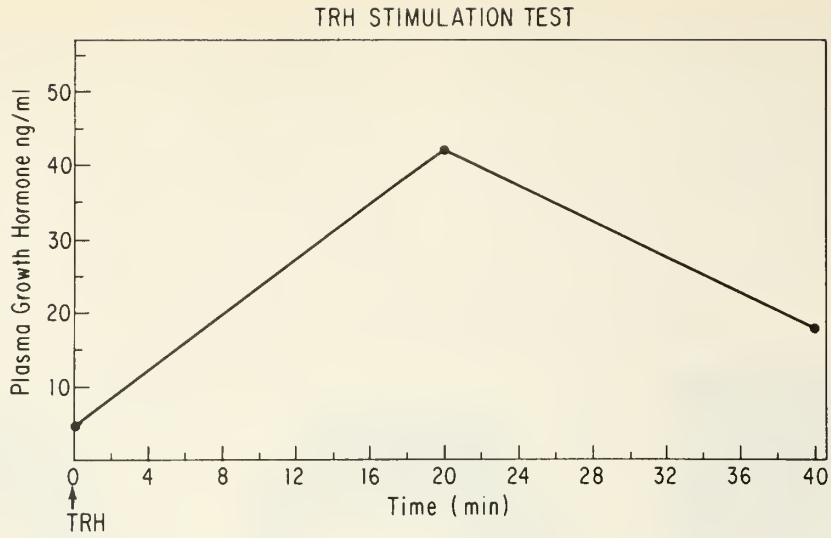


Figure 2. *At Time = 0, 500 ug TRH are administered to the patient in a supine position over 15-30 seconds. Plasma growth hormone is measured at time 0 and at 20 and 40 minutes. In normals, growth hormone secretion is not stimulated as opposed to the paradoxical response shown in this figure.*

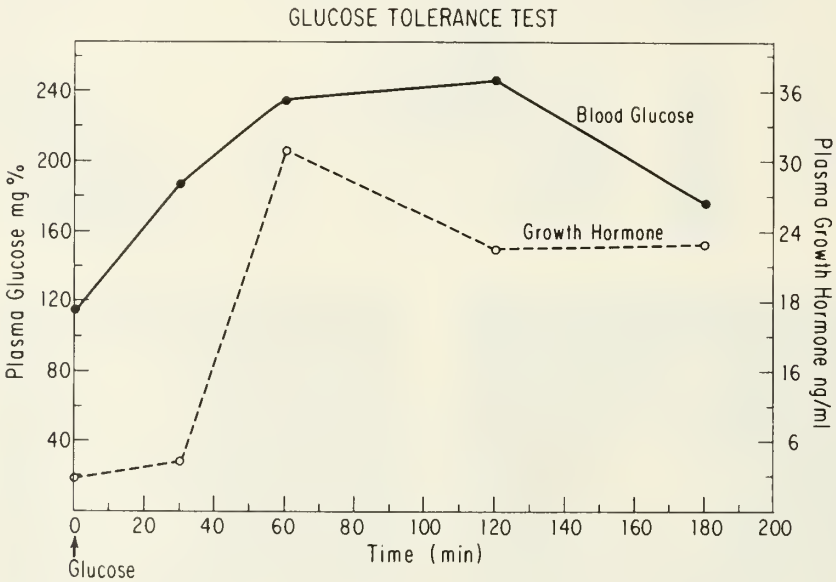


Figure 3. *At Time = 0, 100 g of glucose is given by mouth and serum glucose and growth hormone levels are measured at times 30, 60, 120 and 180 minutes. In normal patients glucose suppresses growth hormone secretion but a paradoxical response such as the one depicted in this figure is noted in acromegalic patients. Notice also the mild glucose intolerance with a two hour post prandial blood sugar of 240 mg/dl which is fairly common in acromegaly.*

agnosed acromegalic would walk into my office, given that the disease occurs approximately once per 25,000 people and between 60 and 90% of these people die by age 60, often of hypertensive and cardiovascular complications? The answer was practically nil! Most endocrinologists at Duke have seen only a handful of these patients in years of seeing a referred, sub-selected group. But my curiosity was piqued nonetheless, so on her return visit my clinical skills were more acutely sharpened for a potential diagnosis. I enlisted the service of several colleagues more experienced than myself and after gazing upon D.B. and hearing the story her diagnosis was "obvious," so I'm told. Upon closer questioning, D.B. had had arthritic symptoms for years and had been shuffled through the medical grind at various institutions with prescriptions that had included physical therapy, steroid injections and various analgesics. Her history was remarkable otherwise for some cardiac rhythm abnormalities and bilateral hearing deficits. Upon specific questioning she admitted to growing out of her high school ring as well as numerous pairs of shoes. Her



Figure 4. *The white arrow is pointing to the characteristic spade like distal tufts on this hand radiograph typical of the syndrome of acromegaly.*



Figure 5. *Lateral foot films of the patient, D.B., with black arrow showing heel pad thickness of 26 mm in this case. The upper limit of normal for females is 21 mm.*

story, as well as her physiognomy, were certainly consistent with acromegaly (Figure 1) but now, as her physician, it was incumbent upon me to prove this hypothesis.

The workup of acromegaly, I'm sure, does not lie on the tip of every clinician's tongue. Most of us know that acromegaly is a disease of the pituitary, usually an eosinophilic adenoma of the anterior pituitary, which produces an excess of growth hormone. Growth hormone, through the intermediary action of somatomedin C stimulates various tissues to grow. The obvious diagnostic test then is to measure growth hormone levels and, in nine out of 10 cases of acromegaly, these levels are elevated (greater than 5 mg/ml) but in 10% of cases they are within normal limits. D.B.'s fasting growth hormone level was 2.9 mg/ml which is clearly within normal limits. The key point here is that, even when the fasting level of growth hormone is normal, most acromegalics will have abnormal dynamic responses to several physiologic manipulations including glucose tolerance test (figure 2) and TRH stimulation (figure 3). Figures 2 and 3 show D.B.'s growth hormone response to glucose load and to TRH stimulation. Both should suppress growth hormone in people with normally functioning pituitary glands. In D.B. there was a paradoxical rise which is characteristic of the autonomous, growth hormone-producing adenomas present in acromegaly.

Recently it has been found that serum concentrations of the effector of growth hormone, somatomedin C, are a better indicator of integrated growth hormone activity than is a single growth hormone measurement. D.B.'s somatomedin C level was 3.5 u/ml (normal for females being 1.8 u/ml). We hope to be able to follow the level of somatomedin C to monitor disease activity during treatment.

Findings related to this patient's acromegaly include spade-like distal phalangeal tufts on hand radiographs (figure 4) and thick heel pads on lateral foot films (figure 5). Her heel pads measured 26 mm; the upper limit of normal for females is less than 21 mm. She had mild glucose intolerance with a two-hour postprandial glucose level of 246 mg/dl. Glucose intolerance or even frank diabetes is fairly common in this disorder. Her ECG showed frequent premature ventricular beats and her chest x-ray revealed an enlarged heart, both of which are not unexpected in acromegaly. Interestingly, lateral skull films and computed tomogram of the head showed no sella turcica enlargement, implying that the functioning pituitary adenoma was not large. Consistent with this supposition was our finding that other pituitary hormones including luteinizing and follicle stimulating hormone and prolactin were all within normal limits for a postmenopausal woman.

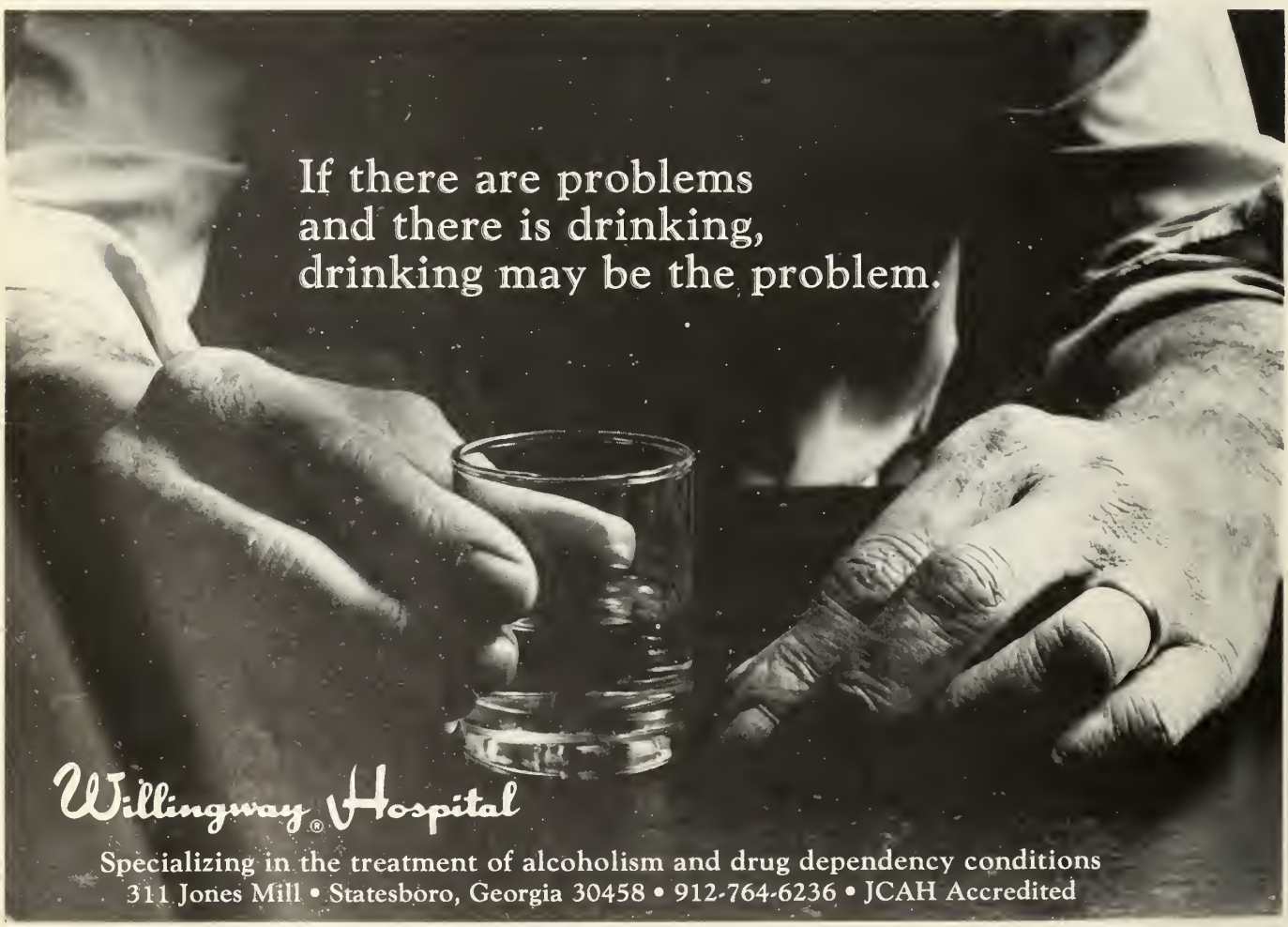
Given this patient's advanced age and symptoms limited to rheumatologic problems — a common presenting complaint for acromegaly, by the way — I elected not to treat with surgical extirpation via the transphenoidal approach. Instead we used radiation therapy in conjunction with bromocriptine, a drug which lowers growth hormone in some patients with acromegaly. As an outpatient, D.B. received 5000 rads of radiation focused on the sella and fractionated over 30-day period. She takes 7.5 mg of bromocriptine a day. After she lost 30 pounds, her major problem, hip pain, was treated with bilateral hip replacement.

D.B. taught me a lot about stepping back and viewing the patient broadly rather than narrowly addressing a single problem. She is a remarkable example of how the medical system can overlook a disease that is rare yet so easily diagnosed simply by thinking of it. Once you see one acromegalic, the next one, if there is one, will not slip through your hands. She also demonstrates how knowing the physiology of a disease process allowed the diagnosis to be made — i.e., by dynamic testing rather than being satisfied with a normal resting growth hormone level.

Finally, D.B. taught me to treat the last clinic patient of the day like the first one, with an open mind.

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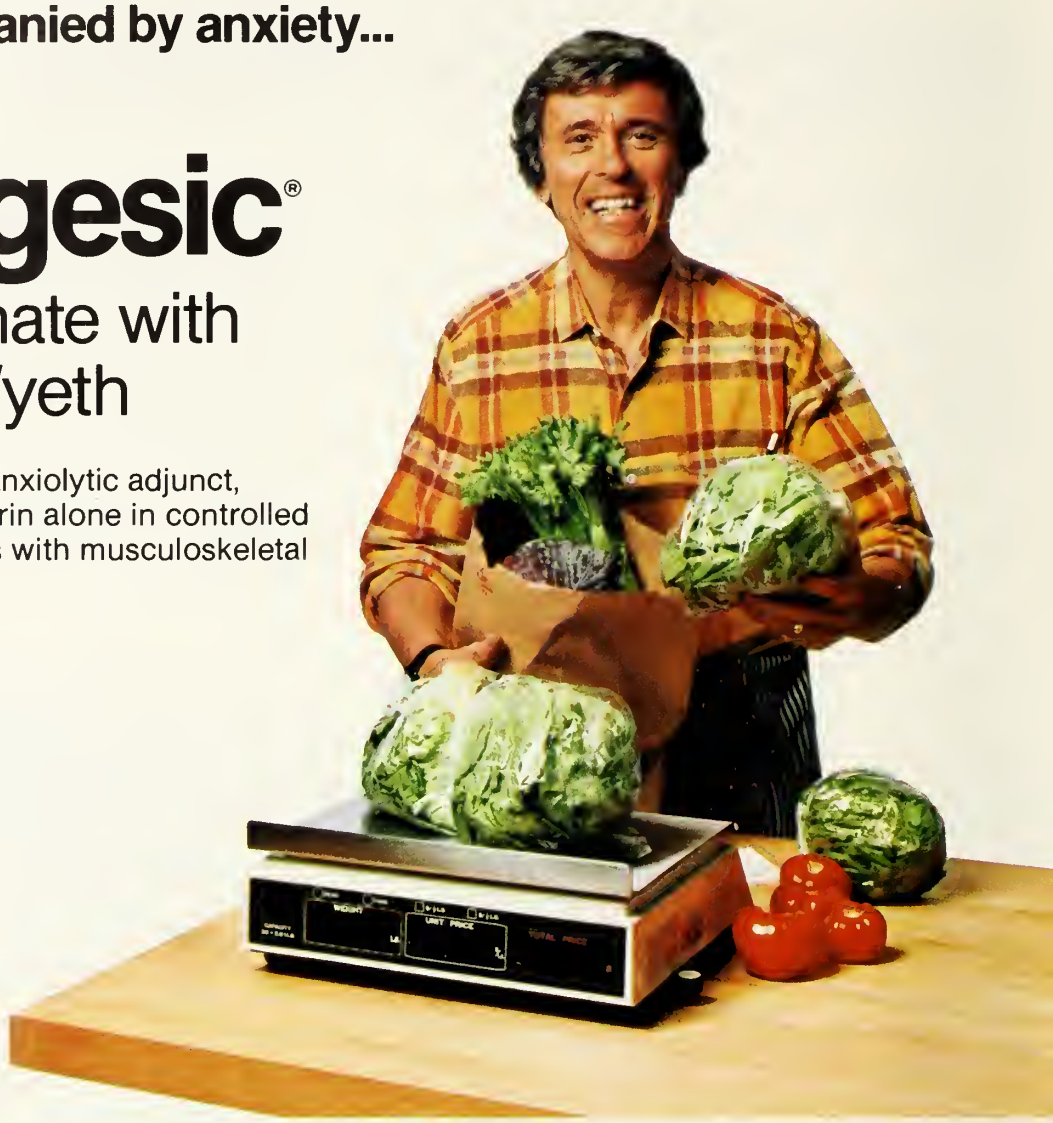


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WARNINGS:
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POTENTIALLY HAZARDOUS TASKS Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e g , driving or operating machinery

ADDITIVE EFFECTS Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously

USAGE IN PREGNANCY AND LACTATIDN:
An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a women of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug

Meprobamate passes the placental barrier It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN Keep preparations with aspirin out of reach of children Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under

PRECAUTIDNS:
ASPIRIN Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics

MEPROBAMATE Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation Meprobamate is metabolized in the liver and excreted by the kidney, to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function Meprobamate occasionally may precipitate seizures in epileptic patients It should be prescribed cautiously and in small quantities to patients with suicidal tendencies

ADVERSE REACTIDNS:
ASPIRIN May cause epigastric discomfort, nausea, and vomiting Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur Patients receiving large doses of salicylates may develop tinnitus

MEPROBAMATE CNS Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity

GI Nausea, vomiting, diarrhea

CARDIOVASCULAR Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis

ALLERGIC OR IDIOSYNCRATIC Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin Other reactions include leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate/mebutamate and meprobamate/carbromal Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis Stevens-Johnson syndrome and bullous dermatitis have occurred

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC") Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura

OTHER Exacerbation of porphyric symptoms

DDSAGE AND ADMINISTRATION:
Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present Not recommended for patients 12 years of age and under

DVERDOSAGE:
Treatment is essentially symptomatic and supportive Any drug remaining in the stomach should be removed Induction of vomiting or gastric lavage may be indicated Activated charcoal may reduce absorption of both aspirin and meprobamate Aspirin overdosage produces usual symptoms and signs of salicylate intoxication Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole-blood transfusions Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse Some suicidal attempts have been fatal The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported Acute simple overdose (meprobamate alone) Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams

BLDDD LEVELS:
0 5-2 0 mg percent represents usual blood level range of meprobamate after therapeutic doses The level may occasionally be as high as 3 0 mg percent

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdosage, such as stupor or light coma

10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment Some fatalities occur

At levels greater than 20 mg percent, more fatalities than survivals can be expected

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol) Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels Any drug remaining in stomach should be removed and symptomatic treatment given Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate Alkalinization of the urine increases excretion of salicylates Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption

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North Carolina Medical Journal

Features for Patients September 1984

Medical Mystery And The Whistle Blower

Mebane H. Burgwyn

Mebane Burgwyn is a remarkable lady whase "projects" have included writing boaks far children, serving an the Baard af Trustees of the University af Narth Caralina, and counseling students in the public schaals while helping ta run Occaneechee Farms with her husband and raising faur children. When her cancer was discavered almast ane year aga, we asked her ta begin anather project: writing an accaunt af her chematherapy and recavery. Her story which fallaws is unlike anything we have published befare in the North Caralina Medical Journal. *We hape yau like it.*

The Editars

In retraspect, thase first maments in the dactar's private affice seem brief, yet endless — as if there were na beginning, anly infinite stretches af time that reached dawn a lang carridar leading ta a cancealed daar taward which I was maving with the dream-like quality af slaw matian. I saw the impact af shack an my husband's face, a paling af his sunbrawned skin, pain in the dark, slightly haaded eyes, and I was acutely canscians af cancern in the doctar's grey eyes behind silver-rimmed glasses. I saw his sensitive mauth beneath the trim grey mustache speaking wards he did nat want ta utter. Thaugh his voice was evenly madulated I felt his reluctance ta tell us what the tests had shawn.

My awn reactian was incredibly law-keyed, unshaken. The beautiful batik hanging in bald tanes af black and rust and ivary, suspended alang the far wall abave the heads of these twa men wha were extremely impartant in my life, seemed the majar facus af my attentian. A neat display af baaks filled the shelves behind Dr. Francis, cantrasting with the littered desk behind me, a disarder which was the undeniable evidence af a man whase prafessianal life was filled with interruptians by insistent needs af his patients, including my awn cries far help during the eighteen manths he had searched far answers ta my perplexing questians. He had spent cauntless haurs studying the valumes af recards fram several haspitals, trying ta find same thread of consistency, same clue upon which to hang the cause af recurring symptams that had fallawed a lang and painful callagen vascular disease suffered in April 1969.

It was clear an this Octaber day af 1983 that further tests were necessary and that Dr. Francis wanted na time wasted. Sa, within a matter af slow-motian maments, I was ance again, far the third time in 1983, canfined within the pratective walls af the huge University Haspital.

Any patient wha enters a teaching haspital encaunters varied levels af medical attentian, depending, of caurse, upan the nature and intensity af his illness. Maving clackwise fram perfect health araund a circle taward passible ar ultimate death, a patient at the 90 degree paint af illness, that is, east af the starting point, has a great deal af time ta think.

He is expected, just inside the frant daar to give details af all vital identificatian and insurance infarmatian. Past this barrier cames the jaurney ta ane's assigned raam and, once settled, there cames the intern's chance ta recard the histary of this case (and all preceding cases). It matters nat haw many times this infarmatian has been given, haw detailed the recards

From Route 1, Box 424, Jackson 27845.
Illustrations by Ernest Croige, M.D.
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from oll one's previous hospitolizotions, an enthusiastic intern with eclectic counseling techniques con moke every oche seem the very one upon which hinges the crux of this porticular problem, ond the unwory potient is apt to get carried owoy with the importance of moking it oll very cleor. If the intern stifles o yown, however, bewore. He hos, ofter oll, been up the entire night with other potients and moy oppreciote o shortened version of the history.

Now, with this inquisition over, the nurses begin their visits to toke blood pressure ond give minor instructions. They ore, for the most port, joculor ond pleasant, taking core of o dozen little things to moke life routine ond os pleasant os possible under the circumstonces. It is then that the 90 degree potient hos time to don o gown unless admission wos precipitous ond unexpected, in which cose the arms ore slipped into o sterile thigh-high garment which moy or moy not hove ties to bring it together in the bock. Once tucked beneoth clean obrosive sheets, there comes the opportunity to moke judgment obout the generol stote of the room: size, cleonliness, equipment, efficiency of godgets; to decide which of the nurses will be o chollenge; ond to think obout life in generol, how mony plons ond appointments one should hove conceled ond whotever led to orrival here in the first ploce.

At the 180 degree level, the potient's condition is obviously more criticol so things ore speeded up and thinking is side-trocked, not only by physicol discomfort but olso by frequent visits of both interns and residents for whom this is o good opportunity to find out how well they hove leorned from their professors. Here is the golden gift of chonce for them — on opportunity to moke o discovery obout this illness which moy hove been completely overlooked by doctor or surgeon. Therefore, precious hours, wrested fram endless demands upon their time, ore spent by these young students of medicine trying to find yet another clue os to the couse of this porticulor illness. Even if the potient had the inclination to think, there reolly isn't time.

At the 270 degree level of illness, the doctors and surgeons themselves come by at regulor intervals, going through familior routines thot reveal to them secrets the potient con in no woy hide. Even the blockest truth af ane's soul is discovered, sometimes in total dorkness, with the potient storing obediently at an illusive dot on the opposite wall. Blood vessels inside the dork pupil of on eye can become relentless lie-detector devices through which the doctor determines whot right the patient has to occupy the bed in this room. Reflexes, obsolutely beyond control when the rubber bludgeon thumps criticol points of the limbs, become tottletoles. Thought by the potient in this condition is errotic ond sometimes irrelevont.

Three hundred ond sixty degrees could be, of course, the end of the beginning or the beginning of the end. Thinking is out of the question as the potient is rolled on o sonitized stretcher immediotely into Intensive Core cr is pretty soon wheeled discreetly out to moke room for new arrivols.

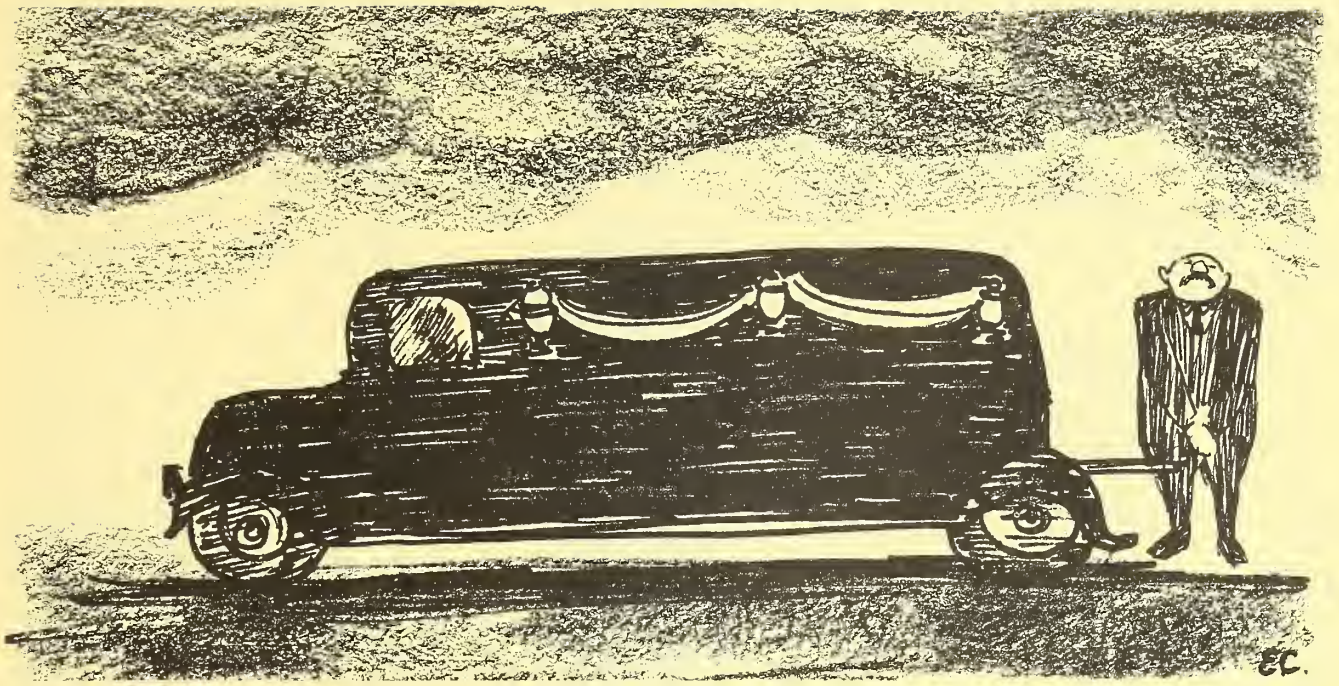
Bock in April of 1969, I entered the Roonoke Rapids Hospitol somewhere between the 270 and 360 degree levels ond for two weeks wos wotched over day ond night by all kinds of people who come ond went — relotives, friends, doctors ond their consultonts ond even drifters who wondered in while they were woiting to see other patients. One stronge lady who come by every doy said ta me during ane of her visits, "I told my Moma lost night you had so mony flowers in here it looked like you was olreody loid out."

I wos, indeed, loid out ond I moy have been ot one of those points af distress that touched my stronge sense of humor becouse the comment struck me os so funny I loughed everytime my wondering mind focused upon it.

I was laid out with olternoting chills ond fever — 105-106, chest pains, legs and orms and former abdominal scors covered with bruise-like spots thot were extremely poinful. Scorlet hemorrhoges blotted out the whites of my eyes; mouth and throot were covered with poinful white lesions, lips so crusted ond dry that milk wos the only food I could tolerate. Hollucinotions removed me occosionally from oll pain ond caring and, upon ony slight elevotion of head and body, I blocked out so completely thot it wos impossible to get X-rays in o stonding or even o sitting position. There wos no orguing the fact that I wos loid out.

A greot deal of octivity went an in order to discover the cause of this sudden physical breokdown of a potient who only one week eorlier hod been enjoying totol heolth. Doctors from other hospitols were called in but with no diognosis forthcoming and my condition opporently worsening, I wos sent ot the end of two weeks to Memoriol Hospital in Chopel Hill. Thot trip wos memorable to me only becouse I wos sent in o funerol-home ombulance insteod of the hospitol ombulonce, which hoppened to be in use ot the time. I would not hove known the difference hod I not, enroute, suddenly needed to urinote. Such vehicles ore not equipped with life sustoining devices for any emergencies of this type ond the poor funeral director who hoppened to be a friend wos forever humilioted becouse he had no focility for toking core of my porticulor need on this occosion. He told me much later thot he olwoys corried o bedpon ofter that olthough I wos never oble to imagine whot eorthly use it cauld be to the clients he usually conveyed.

After my sister-in-law, Morgoret, who wos riding with me found o discorded flower vose, thus providing me with o vessel that was odequote if not comfortoble, I found the incident helpful for it diverted my feverish brain into on omusing troin of thought. My brillionf ond coustic fother-in-low, thot Superior Court Judge who on on occasion hod be-



"I thought I told you not to get Lucius for my funeral. It seems you could have honored my simple request."

come very ill, stated quite clearly to his gentle, fun-loving wife that in the event he did not live through this illness, he wanted her at all costs to avoid having Lucius Northrup handle his funeral or transport him to his grave. When his illness grew worse and his doctor finally administered penicillin, the Judge suffered a severe reaction and went into a coma. Immediate ambulance service was imperative. Unfortunately, Mr. Northrup's vehicle was the only one available for the emergency. As they rolled the Judge outdoors on the stretcher and were sliding him into the ambulance, Judge regained consciousness momentarily and looked up to find the mortician bending over him. Though he was too ill to rise from the stretcher, he called out to his wife, "Josephine, I thought I told you not to get Lucius for my funeral. It seems you could have honored my simple request and found somebody else to do this."

With these and other thoughts teasing my illogical state of mind enroute to Memorial Hospital, I survived the trip barely conscious, remembering very little of what took place during the next several days — or weeks. My life had no relation to time.

Four more weeks of intensive tests in Chapel Hill proved equally as frustrating to the doctors there. Hesitant to administer medication when the tests presented conflicting and divergent results, the doctors were attentive but unreassuring to my husband and family and they sometimes seemed frantic. Their relief was clearly apparent when I suddenly began to improve "in spite of and not because of us," the doctor in charge of my case told me.

My recovery was extremely slow, especially my effort to walk on feet that were unbearably sore as if all tissue under the soles was bruised. The waxed floors of the hospital corridor became a pit of red hot coals. Although I was told this still undiagnosed illness included vasculitis and nerve damage, I did not know until two years later when I was referred to a rheumatologist at Duke Medical Center, that I had suffered a collagen vascular disease which still could not be diagnosed because the syndrome of symptoms was different from any that had been seen at either of the hospitals where I had been a patient.

Under this doctor's care I became stronger; yet problems continued to plague me. There was a bronchial infection which led to the partial collapse of one lung and, in the summer following that, a bladder operation. My vision was affected and I gradually lost more than fifty percent of my hearing acuity. Two years later, I suffered what was called a toxic reaction to medication given for cystitis and had a two-week stay at Duke Hospital while they searched for reasons that were not forthcoming. The next year, Dr. Williams removed a defunct gall bladder and sometime later there was what appeared to be a recurrence of the collagen disease with all the painful symptoms reappearing, though in a milder form.

Within a yeor I wos bock at Duke with severe obdominol pain ond o high amylose count which might indicate problems of the poncreos. I was convinced that I was coming oport, piece by piece, like the 1959 Plymouth convertible we once allowed our sixteen-year-old son to hove ond which my husband sweors he reploced, port by part, except for the steering wheel.

Twice during this yeor of 1983 I had been in the hospital for CAT scans becouse of abdominal pain ond twice had been dismissed, leaving bath Dr. Froncis ond his potient less thon sotisfied with test results. Then, whot wos I doing here, my aching body once more tucked in o white sterile bed, my spirit fettered like broken wings? The answer to this was Dr. Froncis. He wos not a doctor who gove up easily; nor wos he one who dismissed poin as a figment of the imoginotion.

He ordered another ultrosound test ond the lorge moss was found, confirmed loter by another CAT scan. A biopsy followed, indicating moligNant cells, and then came surgery to remove a section of the moss in order ta determine the type of cells thot must be treoted. With the diagnosis finolly completed, Dr. Francis ond Dr. Gordon, the hemotalogist he had called in to toke aver my case, come in and sot down to discuss my situation — to give me answers that come almost os a relief.

The mass, a lymphomo located in the obdominal cavity, had been missed in both previous CAT scans, ane being too high, one tao low. Haw long it had been there grawing silently, insidiously, wos impossible to say. How much it had contributed to other difficulties wos impanderable. Whether it wos o cause ar o result or had onything to do with the collegan vascular illness was a motter of conjecture, but there it was — a problem that wos definite ond treatable.

I was nat promised a hundred percent chonce of recovery, neither was I given any promise of o rose garden far the months ohead. But I was given a chaice — six months of treatment with the outlook on the plus side of bright for this type of cancer, or —

Well, there was no choice. My husbond olwoys spoke of my voried interests as "projects" and wos both amused ond tolerant of my efforts whether it might be writing, ort lessans, guitar lessons, teaching, cross-stitching, or working with various state ond locol boords. Now, I hod been given the ultimote project. The odds were in my fovor, whotever the cost in side effects. Hod the coin come up on the flip side, my thinking would undoubtedly have token different directions. I would hove hod to gear myself to making eoch doy count. I would hove hod to dig deep for ways to cope. As things were, I wos being promised uncomfortoble side effects, loss of hoir, six months of some kind of hell. But the chance of recovery beckoned me like o bright and shiny stor. Chemotheropy. Whot o golden word of hope that seemed to be. Perhops my thin stroight hoir might even grow back lustrous and curly. It seemed o dreom worth dreoming.

My initiol visit to the Oncology Clinic while I was still recovering fram surgery gove me o shock. From my wheelchair I looked out over the lorge reception room. There were thirty-seven choirs ond all of them were occupied, most of them by potients woiting to be seen, some of whom were so obviously ill that it seemed I might be the most fortunote omong them.

In the womens' bathroom o pretty, stylishly dressed lody apologized becouse she wos crying.

"Please don't opologize," I soid. "I understond. I hove reoson to cry, too."

"I guess everyone here does," she soid, wiping her eyes.

It occurred to me as I left her, still teary, that I hod not cried. Not once had I cried. Maybe I was strange, not to have cried.

At the admission desk, I was given a sheof af records and instructions stopled together ond was told to take them to the lab technicians. In the lab, sameone took the papers ond tald me to woit outside until I was called bock for blood work. From thot moment I learned very quickly thot waiting would be on importont port of the treotment.

Seated in the reception raom, I looked about me ot pale foces; ot the missing eor ond the bold heods of men who ware no wigs to cover their bore white skin; ot the young girl, just budding into womanhood, who wore o bondona kerchief to hide the brand that morked her os one of us. It wos then thot the waiting become toleroble. I knew thot I wos waiting because the doctors were oddressing their attention to the urgent needs of these people as their nomes were colled and thot I would receive the some unstinting care ond interest when my time come for consultation.

You waited to be colled back inta the lab where blood wos drown ond checked carefully by the doctar before he saw you. Then you reported immediotely to the nurses' statian for a recording of weight ond temperoture after which there wos onother woit until your dactor wos reody to see you. This could be fifteen minutes or two hours. Once in his exomining room, however, the omount of time he spent with you wos governed by your individuol need. There was never a sense af haste or pressure of time. His exominotion was tharough with coring attention to every comment or complaint or question written down during the week ot home. If there was a problem reloted to o specific field of medicine, a specialist in that area was called in as o consultont.

After this exominotion, the doctor then sot down again and gave a full evaluotion of your condition with a discussion of your treotment for this day ond the week until yaur return visit. You knew whot you might expect and thot you could call for help anytime during the twenty-four hours af any doy. Usuolly, I left Dr. Gardon's office with an upbeot reoction, encouraged and reinforced with determinatian to get through this treatment and the seven days until

my return.

Back in the receptian raam after the dactar's examinatian, yau waited far yaur turn in the chematherapy lab. There were three technicians wha administered treatment ta patients in three reclining chairs and ta thase wha might be accupying the three beds in an adjaining raam. There was alsa a space at the desk just inside the daar far thase patients requiring anly brief treatment.

That first day Elizabeth, a petite, brawn-eyed blande with brisk and bauncy goad humar, gave me pamphlets related ta cancer in general and lymphama in particular. She then cavered me with a warm blanket and handed me a candy lazenge ta suck while she sat by my reclining chair and administered the cantinuaus flaw af saline salution and the chemicals that I wauld be getting ance a week far twa weeks. I understaad that fallawing these twa weeks, I wauld be given a different cambinatian af drugs twice, ance each week. Then this faur-week cycle wauld be repeated and the entire series wauld be given in six cycles, all tailared by Dr. Gardan, far my particular needs. Twenty-faur weeks. Six manths. It seemed an eternity.

With the medicines flawing inta my veins, I saan realized that the candy was designed ta cover up the strange and unpleasant metallic taste that pervaded my body.

"This vial cantains Decadran and it will make yau feel a prickling sensatian in the vaginal area far just a minute. It's given ta prevent nausea that the chemotherapy may cause," Elizabeth told me as she pressed the plunger af the syringe. "And this ane," she said, picking up a larger syringe filled with red fluid, "is Adriamycin, the first af the three anticancer drugs yau'll get taday and next week. This will make yaur urine turn red and it's the ane that makes your hair came aut."

"And when can I expect that ta happen?" I asked her.

"By the third week yau can expect it ta fall aut by the handful so stap by the K-Mart an yaur way hame and buy yaurself one af their wigs. They're inexpensive and very attractive. Dan't mave," she cautianed as I shifted my pasitian. "If this fluid gets an yaur flesh, it will burn yau."

"But yau're putting it into my veins."

"I knaw. That's just where we want it."

"What is this stuff, anyway. Where daes it came fram?"

"It cames fram sail fungi and is suppased ta black cancer cell grawth."

I watched her monitar the saline salutian which was being given simultaneausly and then saw her replace the first vial with anather smaller vial af Vincristine, a drug derived fram the periwinkle plant. It, taa, she told me, interfered with abnarmal cell divisian as did the third chemical, Cytaxin. These three drugs in combinatian, I learned, seemed ta be mare effective than any ane af them alane would be. It was true that alang with destraying cancer cells they alsa destrayed white blaad cells that are sa vital in fighting infectian. This was the reason far making a twa-week change in treatment and switching ta two different drugs — Bleomycin, given by injectian, in cambinatian with Prednisane, taken arally each day at hame for faurteen days. These twa drugs alsa destroyed cancer cells but wauld nat attack certain white cells, thereby giving the bady a chance ta build up a replacement of these cells.

Upan release fram the haspital after my secand treatment, I was happy when ane af aur three sans arranged ta make as easy as passible a quick faray inta the K-Mart an aur way home. He helped me ta find and assess the display af wigs and then staad aff at a distance ta judge each af them as I tried them on. I staad an shaky legs in frant af a tiny clauded mirrar seeing myself became persans



"With a little more out in front, you might be Dolly Parton."

I did nat knaw and, suddenly, I felt that this was a remarkable mament in my life, a mament of priceless fun shared with my san, a fleeting mament snatched fram pain and illness to be enjayed and remembered.

"That's it. That's the ane," I heard Henry say. "With a little mare aut in frant, yau might be Dally Partan."

The wig was shart, curly and slightly blander than my awn hair. Althaugh there could be na illusian about my resemblance to the beauteaus Dolly, I was satisfied that my appearance in this wig wauld nat be a completely shacking departure fram my natural hair. Sa the purchase was made and I callapsed amid pillows when we were ance mare enraute hame with the camfarting thaught that my appraaching baldness cauld be camauflaged by an abundance af blande curls.

Before the third week and the loss of hair, hawever, I faund myself being transparted back ta Duke Haspital by the local Rescue Squad. Far five days I remained there while Dr. Gordon had me treated far nausea and fainting and taak precautians ta protect me from infectian as my white blaad count had dropped dangerausly law.

Back at home fallawing my third treatment, this time with Bleamycin, I dutifully swallawed the Prednisane pills each night and morning and saon realized that the side effects af this cambinatian were gaing ta be even less pleasant than the first treatments had been. Chills and fever, which I was tald might be avaided if I taak Benadryl and Tylenal, accurred anyway and when I tried ta walk ar ta feed myself, the palsy-like lass af muscular cantrol was disconcerting. Equally as hard ta bear was the pain that shot through glands in my neck behind and up towards my ears whenever I ate or drank anything, even water. It was as if I had a smashing case af mumps.

"Cut the dosage of Prednisone in half. Just take ane pill a day instead of twa," Dr. Gordon told me when I called him on the telephone before my return ta the haspital far a faurth treatment. He alsa discantinued three af the faur Elavil pills he had prescribed ta stabilize maad changes he thaught I might experience in having chematherapy. Even this did nat campletely stap the shaking ar the drap in blood pressure and the fainting spells when I attempted ta stand ar walk. Once in the night I fell in the bathraom and bruised the side of my face sa that I became fearful af trying to walk alane.

I was well inta the secand manth af treatment when I awake ane night feeling strangely numb and debilitated. My left side felt paralyzed. I sat up in a state af panic and turned an my light. My heart was barely beating against my chest; the pulse was very slaw and irregular. I tried ta stand and fell, weak and faint, back anta my bed. I laaked at the clock. Faur a.m. The witching haur. The time when many babies were barn, when ald peaple died, when athers took a turn far the warse. Was I dying? I certainly felt that I was. I cauld nat just lie here and die. There were still a lat af things I had ta da. I tried again ta stand. Impossible. I struggled ta sit up and then reached for the blaad pressure kit with which I had been keeping a recard far the dactors. With the cuff adjusted, I pumped the bulb. 58/52. Haw law cauld blaad pressure ga before yau died? Wha cauld I ask? My husband was asleep in the next raam, but he would have na idea about this. I laaked at the telephane. Dr. Gardon had said I cauld reach him twenty-faur haurs a day. I needed ta know. My hand clased aver the receiver and I dialed the number.

A strange yaung vaice answered when I gave my name and identified myself as Dr. Gordan's patient. "This is Dr. Andrews speaking. Can I help you?"

"I just want to knaw if I am dying," I said.

"Tell me. What's your problem?"

"My whale left side is numb. My heart is hardly beating. I can't stand. I faint. My pulse is weak and my blood pressure is 58 aver 52."

"Well, tell me wha took yaur blaad pressure."

"I taok it," I said.

"Well, Ma'am, if yau can take yaur blaad pressure, yau're nat dying."

I was silent far a mament, pondering the lagic af this. "That's all I want ta knaw," I said. I laid the receiver back inta its cradle.

There was na real physical camfart ta be faund anywhere, hawever. Anather side effect had entered my life making my days almast unbearable and my nights af restlessness no periods far relief. I began to hear music perfarmed far me twenty-four haurs a day by a splendid charal graup lacated within my head. The mixed vaices were clear and in perfect pitch as they sang sangs from aut of my past — sangs I did nat even remember that I knew: Baptist hymns, Episcapal chants, patriotic sangs, "Anchars Aweigh"; popular sangs, "Yau Needed Me"; falk sangs, "I've Been Warking On The Railraad"; cauntry and western songs, "You're Always On My Mind." The maddening thing about the music was that, ance started, each melady was sung thraugh and repeated endlessly, relentlessly, never ceasing, never changing until I, driven ta distractian, cancentrated upon a mental switch ta same ather tune. Even then, the melady aften slipped back inta the tune I saught to escape.

Other develapments were taking place. True ta schedule, my hair was caming out and the process was not entirely painless. My head was distressingly sare to tauch, and prafuse sweating left my pillow soaked. Each morning I awake ta find maunds af hair an my wet pillaw and pulled wisps af it from my mouth, saw white skin of my bare head begin to appear beneath the fine gauzy residue that defied the chemicals and remained as token salve to waunded pride. I cut this fuzz shart and covered it with the wig.

"I declare, you laok better than I've ever seen you look," a guest would say. Though this gave me a degree of pleasure, it was tempered with

doubt.

"Nobody would ever believe you've been sick," onother would comment. Absolutely no credit for oll those side effects.

"You look wonderful!" Amozement in the tone.

Although my mirror revealed o darkening of skin color ond o moonfoce coused by Prednisone, I wos aware thot my friends' reoction wos born of kindness. Nevertheless, I begon to think I would wear the wig forever. It certoinly meant instont improvement without effort. But then, one Sundoy morning, a glonce in my mirror brought dismay. All the curls ocross the whole front of my wig were shriveled ond porched os if scorched. Totol disoster! But I hod been oround no fire. What could have hoppened? From the kitchen came the oroma of roost beef cooking in the oven. Of course. It wos steom from the pot when I hod lifted the lid to check the roost. Steam had melted the ersatz hair. Bock to the K-Mort. Pick up another Misty 22 in Honey Blonde.

In the meontime, a fine rosh resembling German meosles appeored on my body from ormpits to groin, on itchy, stinging red rash. During my next visit to the clinic, Dr. Gordon called in a dermotologist so that they might come to some conclusion obout which of the medicines wos responsible. The weolth of side effects I wos presenting was cousing some consternation. They decided thot I should be taken off the remoining Elovil pill ond mentioned the foct thot the Prednisone which I would be getting ogoin would effect heoling of the rash.

"Oh, Goody," I soid, somewhot wryly. "I can rejoice. I'll be wolking oround with Porkinson's Diseose but, never mind, my rosh will be fading awoy." The doctors loughed.

Not so funny, however, wos still another reol problem. The ulcer-like sores in my mouth which mode eating sheer ogony begon to extend down my throot ond talking become difficult. I was hoorse without hoving o cold. The persistent congestion in the bock of my throot and the constriction of my vocol chords, to say nothing of having to listen to my high-pitched voice when I tolked, gove me some concern. Dr. Gordon orronged an oppointment with Dr. Corroll, on eor, nose ond throot speciolist, but there wos to be o woit of two weeks before he could see me.

It was during this intervol thot I woke to find thot the choral group hod deported. I no longer heard their music ond the relief wos immeasurable. Then, too, Dr. Gordon hod odjusted the dosoge of chemicols so thot I wos beginning to tolerate the treotments with less severe chills ond fever or nouseo which olwoys hod followed one or the other of the injections. The shoking wos subsiding ond, finally, the diognosis by Dr. Corroll wos reassuring. The throot problem wos not concer. It was only thot my vocol chords were paralyzed. Ponic. Perhaps the medication wos responsible? Would the condition improve when it wos stopped? We'd just hove to woit for the onswer to that.

Best of oll developments, however, wos the report from the CAT scan thot was done ot the midpoint of my treotments.

"The moss is gone," Dr. Gordon told my husband ond me ofter he hod looked at the X-roys.

"Whot do you meon by 'gone'?" I osked. "You meon completely gone?"

"Yes, there is no longer ony sign of the mass."

I was incredulous. I looked ot him, this handsome, direct doctor whose brown eyes wormed so easily into o smile. "Would you have been worried, would I hove been in trouble if it had still been there or only o little smaller? It's been only three months."

Dr. Gordon, olways honest ond explicit, replied. "If it hod not been reduced in size at oll, I would hove been worried. If it hod been one holf smoller, I would hove been con-



Total disaster!

cerned. If it had been considerably smoller, I would hove been satisfied. But with this result I was very pleosed. It puts yau in the cotegory of those who are most likely ta hove o complete recovery. But we will continue the cycles of treotment as they hove been planned."

My husbond and I ogreed with the wisdom of this and I hod o dreom thot my days henceforth would be more comfortable. But I wos for from home free. Side effects still lurked, hidden ond reody to strike in unexpected woys: side effects from antibiotic medication used to combot urinory infection, return of chills and fever ond even the music, though it wos more subdued in clority thon before and not as all-pervasive. There were lang nights of sleeplessness, some of them with no sleep ot oll, ond there were the ever-present mouth sores and fever blisters. There was the unpleosont metollic smell ond toste thot followed the treotments, ond a distaste for food os well as the burning of my digestive system when I did eot anything. My body felt buffeted and electric with protest os the chemicals continued to course through my veins. I visuolized the battle going on inside my body with concer cells screaming in fury os they were ottacked by the onti-cancer drugs. I become the cheerleader for those chemical worriars thot were fighting in my beholf. My proyers were for their victory ond for couroge and endurance to contoin the conflict ond to get through eoch week, eoch doy, each hour.

I read ond looked ot television. I cooked exotic food which hod no oppeol for me, and welcomed visits of family and friends who come bearing gifts of lave ond good wishes. Occosianolly, I went out for o meol with my supportive husbond who hod eosed the pressures of my life in so mony woys but, generolly, during those winter months, I welcamed the worm haven of our fireside and the view fram our boy window, wotching cordinols, chickodees, evening grosbeoks, finches and ather beoutiful birds that came to aur feeder ond bathed in the heoted birdbath. And there were alwoys speciol times when our concerned sons ond cherished doughter come to help or to visit, bringing with them their lively fomilies, filling the house with fresh young viewpoints, loughter ond teosing. Through all of it, I felt the pawer and wonder of God's love. I was grateful for His gifts thot mode heoling passible, for the skill ond patience of Dr. Gordan who knew how to use the gifts ond for Dr. Froncis who wos so persistent, in the first ploce, in his search for answers to my problems. I was touched by the prayers of my family ond my friends who eoch week taok turns transporting me the hundred miles to Duke Hospitol and returning me home, often prostrote on the back seat of the car.

It wos neor the end of my treotments, during the last cycle, thot I talked with resignotion to Dr. Gordon. "It is finolly clear to me," I soid, "thot this is going to be tough every inch of the woy ond I om going to be screoming and complaining right down to the wire."

"Well, good," he soid, smiling at me. "I certoinly wouldn't wont you to change."

So huffing and puffing, I came to the doy of my lost visit with him ond it wos then that I finally experienced the anly side effect listed thot I hod not yet felt. I had heard that word ond reod abaut it in the book thot Elizobeth hod given me that first doy ond had wondered o hundred times why it wos sa lang coming. Dr. Gordon himself hod promised that, omong ather side effects, I would get this feeling from Prednisone, but it had eluded me.

Now, sitting in his examination room while he checked glonds, musculor reactions, heort ond lungs, my body felt curiously loved ond then elevoted by levity ta a glorious feeling that I had been promised. In spite of residuol discomfart, my spirit was flooting obove and beyond all the agony my body had endured. I could recoll the reolly tough doys, remember the fointing, the nousea, the chills and fever, the mouth lesians and vocol problems, the shoking, the music, the glondulor pain, the roshes, the debilitating weokness and generol misery and know that the "project" was now behind me. I wos oware thot I hod never been given any guorontees, but in this moment I could see these past six months os interesting, educationol, rich with humor and new understonding of the trouma and poin thot thausonds of people face everydoy. I could identify with them ond appreciote the need far research to combot this terrible disease thot is so prevolent in our society.

But far one long moment my mind roced for beyond these thoughts ond corried my soul to intrinsic heights of triumph. I could only rejoice in hoving come through the six months of hell that hod been necessary for any hope of recovery.

I looked at this doctor who hod never once wovered in his cancern for my problems or for me.

"You know, Dr. Gordon, I feel like o bottered, overlooded freighter, one thot has just been moneuvered through o storm over dangerous shoals by o very skilled coptoin."

He smiled just a little. "Thot's nice," he said. "It's almost poetic." And then he laughed.

And I loughed, tao, succumbing to the sheer pleosure of the lost side effect — euphoria ond a sense of well being.



. . . succumbing to the sheer pleasure of the last side effect.

A Specialized Unit for Patients With Diabetes Mellitus

Ellen D. Davis, R.N., M.S.

What can a person expect when hospitalized for regulation and control of diabetes mellitus? Hospitalization for any reason can pose great problems for the patient with diabetes and even when the explicit purpose is to "improve control" those hazards are not eliminated. Among the potential problems are meals that are institutionally timed rather than conforming to the patient's usual routine, and meal trays that do not appear or must be delayed because of tests. Additional problems include lack of opportunity or facilities for exercise; erratic swings in blood sugar concentration resulting from the stress of hospitalization; and the upset of normal routines of self-care by health care providers. *Diabetes Forecast* (the excellent patient-centered publication of the American Diabetes Association), which has called attention to these problems for several years, urges that patients persist in their efforts to care for themselves and to assist the staff whenever they are hospitalized. Whenever that hospitalization is primarily for control of diabetes itself or for treatment of a diabetes-related illness, admission to a specialized diabetes treatment unit can minimize the problems alluded to above. One such specialized unit is located on Hanes Ward at Duke University Medical Center in Durham. Since many patients are not familiar with such specialized units, I propose to outline the workings of the Duke Unit to acquaint patients with what they may expect from hospitalization on a diabetes unit.

In general, patients gain admission to the unit on referral from their personal physician to a member of the Division of Endocrinology in the Department of Medicine at Duke, although some patients initiate the referral themselves. The length of hospital stay for diabetes control and education is usually five to ten days. As a rule, the costs of hospitalization are reimbursed by hospitalization insurance at the same level as other diagnoses and treatments. After discharge, most patients return to the care of their personal physicians, but they may continue to see the Duke consultant on a periodic basis as indicated. A discharge summary describing the course of hospital care and the recommended treatment plan is always sent to the referring physician.

From Box 3714, Duke University Medical Center, Durham 27710.

Staff of the Diabetes Unit

A patient admitted to the Diabetes Unit will encounter a high level of professional competence and an appreciation of the complex medical and psychosocial aspects of diabetes. The attending physician will be an endocrinologist, a specialist in diabetes and disorders of other glandular organs (including the pituitary, thyroid, parathyroid and adrenal glands and gonads). The attending physician is assisted by a resident, a physician in training who is spending a period of time specializing in endocrinology. Since diet therapy is the keystone of diabetes treatment, each patient is seen by the dietary staff which is headed by a diabetes dietitian-clinician. The nursing staff on the Diabetes Unit have all chosen to work with this patient population and are expert in diabetes care and diabetes patient education. In addition to a head nurse, assistant head nurse and staff nurses, the Unit has a diabetes nurse clinician who has special expertise in patient education; these nurses work together continually to increase their knowledge and skills regarding diabetes. All personnel on the Diabetes Unit recognize that the care of the person with diabetes is a team effort with the patient as the most important member.

Getting a newly diagnosed patient off to a good start

Patients with newly diagnosed diabetes mellitus are admitted to the Unit in order to start them on the road to efficient self-care. Since we believe that the chronic complications of diabetes come from having an abnormally elevated blood sugar over a period of time, we are eager to arrange the best individualized medical plan to achieve tight control of blood sugar. In conjunction with the patient, the dietary staff will derive an appropriate meal plan to reach or maintain ideal body weight. If insulin or other drug therapy is indicated, the medical staff will help work out the details of treatment. The patient is given intensive individual instruction in the principles of diabetes care. Finally, because even the best of plans can have no benefit unless the patients can put them into action in their everyday life setting, the dietary and nursing staffs encourage the patients in self-management.

Helping patients who have had diabetes for many years

Many patients admitted to the Unit have had diabetes for some time. Most have not practiced the primary cornerstone of diabetes management, the individualized diabetic meal plan. Their self-care knowledge and skill need serious tune-up. They may have some of the chronic complications of prolonged high blood sugar and erratic control.

Some patients arrive feeling very ill while others feel relatively well but know that their present level of control will lead to future trouble. The key to leading a long, full life with diabetes is to keep blood sugar levels in the same range as people without diabetes. This may seem an impossibility to persons who have had erratic blood sugar levels for many years but it is an achievable goal. It does require hard work on the part of both the staff and the patients. Patients must be willing to replace old attitudes, information and behaviors with a commitment to a consistent

daily regimen. Patients need always ta remember that the slawly developing chronic complicatians result fram elevated blaad sugar and erratic cantral. It is nat true that complicatians are inevitable; in fact, camplications already started can be helped by normalizing blaad sugar cancentratians and maintaining tight cantral.

Admission to the Unit

After an intensive assessment by the medical, nursing and dietary staffs, the work begins for aur patients. They are encouraged ta bring casual street clathes since we do not view mast af them as sick but as patients in need af reorganization. The educatianal process begins upan admissian. Whether the patients are physicians ar farmers, they are in need af updating on the process of self-care in their unique life settings.

The diabetes nurse clinician or anather member af the nursing staff will explain the gaal and benefits of narmalized bload sugar concentratians and the necessary angaing patient invalvement in gaining control af blaad sugar and maintaining that cantrol in the "real warld." Explanatians are given gently many times aver ta thase feeling stressed by being in a haspital. Medical staff review the pragress taward the gaal af better bload sugar cantral and help the patient to became adept at initiating the changes needed to reach that gaal. Reading materials relating ta the nature af diabetes and the principles af diabetes management are pravided far patients to study.

Patient involvement in education and regimen planning

We tell patients that they need twa things ta live fully with diabetes: the right medical plan and the wherewithal ta put that plan into action, *themselves,* in their day-ta-day life. We teach patients when and haw to test and recard urine sugar concentrations. Often we teach them how ta test their awn blaad sugar concentratian by taking a single drop of blood with a finger prick. Urine and finger prick blaad sugar concentrations are tested four ar mare times a day in the hospital. Patients and staff study these test results ta determine the mast apprapriate medical plan. Patients are involved in understanding this medical pracess and the treatment chaices as well as in learning the perfarmance skills they will need at home. We da nat arrive at a medical plan "in secret" and then keep patients another week ta teach them haw ta maintain it. Patients and staff wark tagether ta arrive at the goals simultaneausly.

Patients wha will be manitaring blaad sugar at hame will need ta purchase apprapriate equipment. The diabetes nurse clinician keeps abreast af the many advances and refinements in this field and can help patients chaase amang the alternatives available to them. The dietitian warks with patients and their families ta determine a meal plan far each individual. We have recently added a teaching kitchen adjacent to the Unit and plan ta pravide hands-on practice in meal preparatian far our patients.

The goals of patient education

Our facus in patient educatian is always to integrate the regimen into the patient's hame life. Creative problem solving abaut hame matters is always encouraged. Typical questions are the follawing: Haw can I test my urine or blaad befare lunch while at work? Haw can I manage an evening out when the meal is going ta be late? How can I accammodate extra (or less) exercise an the weekend than on weekdays? Each of these questians has as many appropriately sound medical respanses as there are people asking them. With a solid backgraund in the nature of diabetes, the aims of cantral, and practical knawledge and skills, patients learn to answer the questians with decreasing assistance from the prafessional persannel. At hame they must handle the recurrent and unfareseen challenges to positive adherence by themselves.

Adjustments of insulin dosage

If patients need daily insulin, their requirements and responses are examined in detail. Finger prick blaad sugar readings give invaluable infarmation abaut haw different types and brands af insulin ar cambinations af insulin wark in individual patients at a particular phase af their diabetes. Each day's readings pravide a look at patients' previaus day's respanses ta canstant dietary intake and the insulin plan in effect. The next day's insulin regimen can then be altered if necessary. All patients learn haw to adjust their awn insulin plan (that is, they learn an "algarithm") in order to maintain cantral at hame. The anly way that tight cantral can be maintained is far the patient ta be knawledgeably in cantral. Fartunately, insulin changes are nat needed often ance patients have attained gaad contral in the haspital, adhere ta the meal plan, and knaw haw ta salve prablems creatively.

Patients learn to draw up and administer their awn insulin. If they have been carrying out this and ather tasks correctly at hame, the review and approval of the staff further increase their canfidence. They alsa learn the newest infarmatian about insulin absarptian and the mast apprapriate sites far insulin injectian. A few patients may benefit fram cantinuous subcutaneous insulin infusian (insulin pump), although the precise indicatians far this device are nat yet clearly defined. In any case, if necessary, patients are autfitted with a pump and instructed in its aperatian.

Exercise and stress management

Exercise is an essential campanent af diabetes care. Street clathes and guidance fram the staff enable patients ta pursue consistent exercise patterns while an the Unit. The physical therapy department as well as farmal, supervised exercise and training pragrams are available and are incorparated as needed. The ability ta carry out actual exercise while an the Unit provides an appartunity far instructian in the preventian, symptams and treatment af hypoglycemia (law blaad sugar) as well as establishing a healthy pattern af behaviar.

Stress can have bad effects on blaad sugar cantral. Persannel an the Unit are aware af the impartance af appraapriate ematianal and psychalagical respanses far persans with diabetes. When excessive ar uncantralled stress limits the adaptatian ta ar cantral af diabetes, we recammend and implement the use af relaxatian techniques, biafeedback training, medicatians ar psychiatric cansultatian as indicated. Of caurse, since the Unit is a fully integrated part of the haspital, cansultatians with physician specialists in aphthalmalagy, cardialagy, arthapedics, uralagy and all ather specialties are available and are arranged as needed. Our gaal is well-informed, educated patients, adapted ta the burdens impased by diabetes and capable af caring far themselves with a little help fram their friends.

Urticaria

Russell W. Eyre, M.D., Claude S. Burton, M.D., and J. Lamar Callaway, M.D.

"Doctar, I have hives." Fartunately mast peaple can easily diagnase this rash because it frequently has disappeared when they see the dactar. Hives, welts, and wheals are all camman names for these itchy, raised plaques with lighter centers and surraunding red patches. The medical term, urticaria, cames fram the latin ward far the stinging nettle plants, urtica. Contact with this plant praduces lacalized hives.

One out af five peaple will have an episade af hives sametime during their life. Most attacks are gane in a few days ar weeks but an unlucky few cantinue ta have attacks far decades. Half af thase patients with chranic urticaria, hives that last langer than twa manths, will cantinue ta have hives five years later.

"Dactar, what causes these hives?" Fluid escaping fram dilated leaky blaod vessels causes the skin to swell. Cells called mast cells release several chemicals that cause the blaad vessels ta leak. These chemicals are quickly inactivated sa an individual spat generally is gane in several haurs. Anything under the sun, including the sun, may cause these mast cells ta release their chemicals. Besides the release af chemicals fram mast cells anything that causes blaod vessels ta dilate may make hives warse. Blushing and flushing fram ematianal excitement, alcahal, coffee, exercise, fever or warm baths may warsen urticaria.

Acute urticaria is aften caused by faads such as shell fish, nuts, berries, eggs, cheese, chacalate ar milk. These causes are usually easily recagnized by the patient and avaided. Rarely the sensitivity is sa great that a minute amaunt is enaugh ta trigger an attack. One lady brake aut after kissing her husband wha had recently eaten shrimp.

Drugs, especially penicillin and aspirin, are cammon causes of urticaria. Dairy praducts may cantain small amaunts af penicillin that may perpetuate an eruptian af hives. Aspirin increases mast cell sensitivity. In ane study farty percent of all patients with urticaria impraved when they avaided aspirin even thaugh they weren't specifically allergic ta aspirin.

Infectians with bacteria, fungi, viruses ar parasites, althaugh frequent afflictians af man, prabably aren't cammon causes af urticaria. In ane study anly faur aut af seventy-eight patients with an infectian and hives were free fram hives after their infection was treated.

Heat, cald, sunlight, water, pressure, and vibratians may all cause hives in same patients. These physical urticarias are easily tested by applying the suspected agent.

Since mast cases af hives clear within twa manths, a detailed search far an underlying cause is unnecessary unless the hives are chranic. Unfartunately, despite the mast expensive and detailed examinatians madern medicine can affer, a cause af hives will be found in only ane aut af faur patients with chranic urticaria. Mast af thase causes are evident after a careful histary and physical examination. Labaratary tests are seldam helpful unless the histary ar physical uncavers anather reasan for parforming them besides hives.

"Dactor, what can I da far these hives?" It's abvious that if a cause such as a faad allergy can be identified that faad should then be eliminated. Occasianally a strict diet will result in impravement indicating an unsuspected faod allergy. All the patient's medicatians shauld be examined including vitamins, laxatives, antacids and other nanprescriptian drugs. Therapeutic trials of antibiatics may rarely reveal a hidden infectian. Eliminate anything that leads ta blushing ar flushing.

Several drugs are available ta caunter the effects of histamine, one af the chemicals released fram mast cells. There are several different chemical classes af antihistamines and an individual patient may respand ta anly ane class. We generally prefer ta start with hydraxyzine but quickly change ta another class af antihistamines ar add anather drug if na respanse is naticed after an adequate trial. A new drug used far stamach ulcers, cimetadine, alsa caunters same effects af histamine and can be a useful addition to traditianal antihistamine therapy.

Other drugs, cammanly used ta treat asthma, such as terbutaline, ephedrine, and theaphylline may help ta stabilize the release af chemicals fram mast cells. Systemic steraids such as prednisane aften clear hives but using prednisone far lang periads is nat justified in uncamplicated hives because af the side effects af prednisone.

The mast impartant therapy af urticaria is reassurance that this disturbing rash is anly rarely assaciated with a seriaus underlying disease and usually anly lasts a few weeks.

From the Department of Medicine, Duke University Medicol Center, Durhom 27710.

EDITORIAL

Training Is No Substitute For Education

Eugene A. Stead, Jr., M.D.

THE current interest in North Carolina to prepare its young people for the work force by vocational schooling makes a review of the differences between education and training timely.

The words *education* and *training* are frequently used interchangeably. We need to appreciate the differences and similarities between these two modalities and not confuse one with the other.

In a narrow sense, education and training have the same goals. Each attempts to establish new learning patterns in the central nervous system which facilitate the performance of new tasks and improve the performance of previously learned tasks. An educational program attempts to produce a wide range of changes in the nervous system and to increase the general capacity of the neural network to store information and to move and rearrange facts. We use the word *memory* to describe the acquisition and storage of information and the word *thinking* to describe the movement and rearrangement of countless bits of information.

The goal of education is to enlarge and extend the many functional neural networks of the brain for greater storage and processing of information. Such networks cover a wide range of content: language, culture, history, art, music, science, feeling states, religion, mathematics, communication, etc. A fully educated brain contains innumerable hooks for attaching, rearranging, and using the information accumulated in the memory system. It can identify problems and solve them. The brain is attuned to profit by history, by knowledge of the great religions, and by the roles that feeling states and culture play in the affairs of man. Education strives to develop a brain capable of enjoying the day and to improve the capacity of the brain to tolerate without hostility the belief systems and behavior of other persons. Education can make the day more enjoyable and the outcome of education is useful when it creates attitudes and feelings that make the day more meaningful. The educational process is not necessarily related to the production of useful things.

Training develops the neural pathways formed by education into well-grooved and well-worn tracks that permit repetitive performances with a high degree of efficiency. Training is aimed at the formation of habits which are so ingrained by repetition that only a minimal outlay of nervous energy is required for performance. Training leads to efficiency over a narrow spectrum; education leads to a broader spectrum of competency.

High school, college, the early years of medical school, and experiences in research laboratories are oriented toward education. Internships and residencies are designed to train the doctor to perform repetitious tasks efficiently. Many postgraduate posts combine research (education) with clinical activities (training).

Our high schools tend to be divided into those that prepare students for college and those that prepare students for direct entry into the work force. The latter are called vocational schools. The graduate from either type of high school will move to areas where it is hoped he will continue to learn. The graduate from high school entering the work force will be trained on the job to perform tasks required by his work. In most instances there will be little time for structured educational programs. His continued education depends on individual effort in an unstructured environment. The only educational capital he has is that obtained during his high school years. He pays a penalty if his vocational high school has sacrificed education for training.

The high school graduate going to college has a better chance of continuing his education, depending on whether the faculty of the college he has selected comprehends the difference between the words *education* and *training*. Eventually the college graduate enters the work force. If his brain has been altered in a favorable way by his college experiences he will be quicker to see opportunities beyond his first job. His college education should protect him to some extent from the rapid changes of our modern society and technology.

At high school graduation we hope that the student has the following attributes:

1. A picture of himself as one who is capable of earning a living in our society.
2. An ability to enjoy the day and not resent the fact that others can legitimately make demands on him.
3. The ability to work with concentration at a task until it is complete.
4. An awareness of time in terms of punctuality and as a measure of efficiency.
5. An appreciation of the fact that the teacher as well as the student has problems.
6. The ability to read English with speed and comprehension. He should be able to understand written instructions quickly and correctly.
7. The ability to communicate accurately by written and spoken word.
8. A quantitative sense which allows him to use mathematics to solve problems and to make accurate measurements.
9. An overview of the arts and sciences which allows him to comprehend books in these areas written for the general public.

From Box 3910, Duke University Medical Center, Durham 27710.

10. An adequate knowledge of history which lets him know the complexity of our social, political and economic systems.

11. An ethical sense which distinguishes between right and wrong and supplies a framework for continued personal growth.

A high school graduate with this educational background can enter the work force of modern society free from fears of obsolescence. Education, not training, protects his future.

Vocational education was formalized because a number of students did not appreciate the need for an educational program and wished task-oriented training which would equip them to earn immediate income. We have always had this problem in medical schools. Some students want to learn only those aspects of biomedical science that are most quickly applied to clinical problems. In the clinical years they wish to be trained for clinical tasks rather than to explore new areas of knowledge which will be applicable clinically in later years. The wise instructor uses the least amount of task-oriented material that is compatible with holding the attention of the student. He leads the student to explore knowledge tangential to the current task and which prepares the student for the future. The faculty know that in most instances the total intellectual capital of the student will be accumulated before he enters private practice. Training continues in practice but education frequently stops.

A recent publication of the National Academy of Sciences[1] entitled *High Schools and the Changing Work Place* addresses the differences between education and training. It emphasizes the weakness of the predominately vocational approach and urges that today's high schools guard against selling the student's educational birthright for a mess of vocational porridge.

Reference

1. High Schools and the Changing Workplace. The Employers' View. Report of the Panel on Secondary School Education for the Changing Workplace. National Academy Press, Washington, D.C., 1984.



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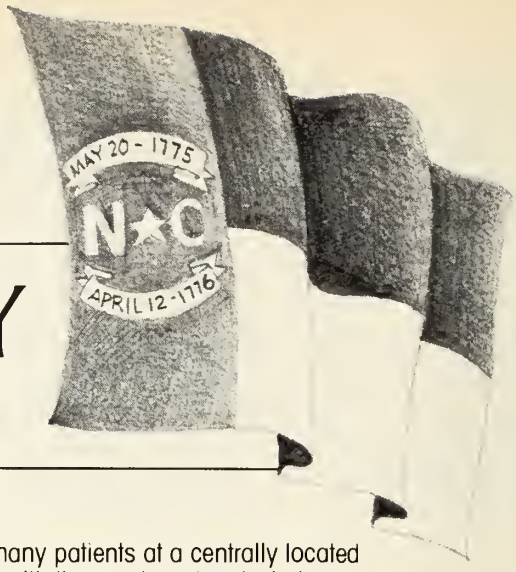
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THE 18-HOUR-A-DAY DOCTOR

Dr. Gaine Cannon

A modern-day version of the country doctor on horseback, Dr. Gaine Cannon covered his scattered practice around the Blue Ridge Mountain country near Balsam Grove, North Carolina, in a four-wheel-drive Jeep wagon.[1]

On an average working day, Dr. Cannon rose at sunup to see patients at his converted-farmhouse clinic before setting out to make his usual 15 to 20 house calls around the countryside. Generally, after treating his primary patient, he saw each member of the family as well—his personal effort at preventive medicine.

Multiple services

With the nearest hospital some 60 miles away and no pharmacy closer than an hour-and-a-half drive, Dr. Cannon filled his own prescriptions, delivered babies and treated many patients at a centrally located general store with the most modern techniques and medications. After a day on the road—usually within a 50-mile radius—Dr. Cannon's office hours would begin at 5:30 p.m. and stretch on until the last patient was attended to. His record-keeping sessions routinely filled the hour before midnight—rounding off Dr. Cannon's 18-hour day.

At all hours

But emergencies often interrupted his sleep. Dr. Cannon claimed his real office hours were 24 hours a day, and his patients revered him for it.

Dr. Cannon died in 1966 at the age of 68. He will be long remembered—most especially by the more than 5000 North Carolinians he helped bring into the world, some of them at the side of a rutted country road.

Reference: 1. Doctor in the bockwoods, in Lee RV, Elmerl S *et al: The Physician.* New York, Life Science Library, Time Inc., 1967, pp. 38-50



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ROCHE

When the history reveals mixed depression and anxiety...

For the estimated 70 percent of nonpsychotic depressed patients who are also anxious,[1] Limbitrol provides both amitriptyline, specific for symptoms of depression, and the effects of Librium® (chlordiazepoxide HCl/Roche), the tested and dependable anxiolytic. Limbitrol is, therefore, a better choice for these patients than dual agents that contain a phenothiazine, a class of antipsychotic drugs which has been associated with tardive dyskinesia.

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Limbitrol also has a rapid onset of action which may lead to greater patient compliance. In a multicenter study, patients taking Limbitrol experienced 62% of their overall improvement within the first week of therapy.[2]

In another multicenter study,[3] the following symptoms associated with anxious depression were significantly reduced during the first two weeks of therapy:

- ☐ Headache—79%
- ☐ Early insomnia—91%
  Middle insomnia—87%
  Late insomnia—89%
- ☐ Gastrointestinal upset—73%

In two multicenter studies, only 1.9% of Limbitrol patients experienced cardiovascular side effects.[3]

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness such as operating machinery or driving a car.

References: 1. Rickels K: Drug treatment of anxiety, in *Psychopharmacology in the Practice of Medicine,* edited by Jorvik ME; New York, Appleton-Century-Crofts, 1977, p. 316. **2.** Feighner JP *et al: Psychopharmacology 61*: 217-229, Mar 1979. **3.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

In moderate depression and anxiety

Limbitrol® 5/12.5 10/25

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see summary of product information on following page.

LIMBITROL® Tablets Ⓝ Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticoria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diorrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

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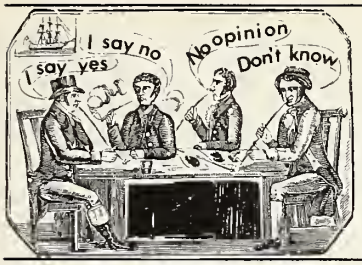
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Cost Containment

Eugene W. Linfors, M.D., editor

The question for September is: **What approaches to cost containment have been successful in your practice?**

From Dr. James E. Davis, a surgeon in Durham.

The following four items are those which have perhaps been most productive in my practice.

1. **Keeping patients out of the hospital.** This, of course, is the greatest increment in total health care costs, and with extensive use of ambulatory surgery, literally hundreds of thousands of dollars have been saved, without sacrifice of quality of care, and almost without exception to the greater pleasure and comfort of the patient. Ambulatory care, of course, is not limited to surgery, and its more extensive use in all fields should be encouraged.

2. **Obtaining necessary diagnostic and laboratory studies prior to hospital admission.** This saves preoperative days in the hospital and actually allows for a better patient evaluation, since any questionable determinations can be repeated, if absolutely necessary, without extending a hospital bill. Again, such prior-to-admission studies are applicable to every field, except for true emergencies.

3. **Anticipating hospital discharge date and discussing it thoroughly with the patient.** Patients' attitudes and understanding of avoiding unnecessary hospitalization have improved in recent years. They appreciate and try to cooperate in arranging to leave the hospital at the appropriate time if this has been thoroughly discussed with them.

4. **Obtaining all current laboratory and radiological determinations from the referring physician.** Though this may require additional time and effort in calling or writing the referring physician's office, it avoids duplication of services and charges.

From Dr. John Glasson, an orthopedic surgeon in Durham.

The doctor members of our professional corporation are acutely aware of the necessity for cost containment in medical care, and we are employing a number of strategies.

To begin with, we are cooperating with the American Medical Association and North Carolina Medical Society in agreeing not to increase our fees for the next year.

We are attempting to minimize patient days in the hospital by initiating discharge planning under the auspices of the Social Service Department at the time patients are admitted. We are also endeavoring to make appropriate use of extended care facilities when needed, and the hospital is enlarging its home health care program in a further effort to promote early discharge from the hospital and a continuum of care in the home setting.

Increased facilities for home health care seem to carry the greatest potential for cost savings when provisions are made for the administration of, for instance, intravenous antibiotics on a long term basis rather than keeping the patient in the hospital for these treatments. Other similar high tech procedures on a home health care basis will offer similar potential for cost savings.

We are also taking care to avoid duplication of laboratory studies and x-rays and are attempting to provide these items for patients on an outpatient basis before being admitted to the hospital in order to avoid the necessity for doing the tests after admission to the hospital. We are also perhaps saving some by using commonly available household items such as old tennis shoes cut out and placed over casts rather than using commercially provided cast shoes purchased in the hospital. We are also attempting to minimize use of disposable items in the hospital as much as possible in instances where safe and effective care for the patient is not compromised.

Our hospital also periodically provides computer printouts of bills for patients' individual doctors in order to acquaint the physician with charge levels for all items and also with the total cost of medical care for typical diagnoses.

In the operation of our professional corporation, we are trying to avoid productivity targets for our physician members, since these tend to put a premium on maximization of charges for the individual patients in order to maximize the individual physician's income.

Probably the most basic effort that we make in trying to contain costs is to maintain at all times the best possible physician-patient relationship. The breakdown of good physician-patient relationships has the potential for creating litigation and the now rapidly escalating premiums for professional liability insurance. These premiums, as you know, are again threatening to produce the failure of one of our professional liability insurance companies and are driving physicians out of certain types of specialty practice or, indeed, entirely out of any practice.

The effort at tort reform in our state legislatures promoted by Medical Society activity in recent years no longer seems to be the answer. It appears that the public must come to realize that these astronomical costs for professional liability insurance are simply passed through in the physicians' charges and it, indeed, is a problem for the public as well as for providers of medical care. Some approach through our medical-business coalition or

through business roundtables could be productive.

Our legislatures are not very sympathetic with the financial plight of physicians with six figure incomes, even when they do have to pay astronomical professional liability premiums. The problem is that the premiums themselves are now approaching five figures in some states.

From Dr. Ira M. Hardy II, a neurosurgeon in Greenville.

As Chairman of the Cost Effective Medical Care Committee for the state Medical Society, I have a strong opinion that outside forces such as medical business health coalitions will have the greater impact on health care cost containment than other cost conscious activities.

As far as my own practice is concerned, our office has adopted the fee freeze requested by The American Medical Association and endorsed by The North Carolina Medical Society. Our office makes an effort to get third party state-supported systems to cover all eligible people whether they are insured or not. This tends to keep the fees charged to these particular people within the guidelines of reimbursements established by that State agency. I am referring to agencies such as Vocational Rehabilitation and Crippled Children.

Our office makes every effort to obtain as many outpatient diagnostic evaluations as we can and we do a considerable amount of ambulatory surgery for minor operative procedures such as surgical treatment of carpal tunnel syndromes.

From Dr. F. Maxton Mauney, Jr., a cardiovascular surgeon in Asheville.

My initial response to this question would be to emphasize the extremely beneficial and "time-effective" utilization of Physician Assistants in our private group tertiary care practice for the past fourteen years. Historically, surgeons have assisted one another during major operative procedures and third party insurers have often paid an "assistant's fee" of approximately twenty percent of the standard surgical fee. We followed this model for many years but as our experience grew and as our volume increased, we began to utilize out of necessity our PAs as first assistants in the operating room. Since third party reimbursement groups would not pay for those PA first assistant services, even at a reduced rate, we did adjust our fees upward to some extent in order to cover a portion of the PA's salary and indirect cost overhead. We have found with increased utilization of very talented, skilled, and experienced PAs that our overall surgical throughput was considerably enhanced. More importantly, with increasing experience we have found that the PA in our practice not only contributes to the overall effectiveness with which an operation is performed, he or she can help shorten the operating time by division of labors! (Saphenous vein harvesting while the surgeon is opening the chest and cannulating the patient, etc., or closing secondary incisions, etc.) While it is very difficult to document an absolute cost saving in this regard, there is no question in my mind that it has been an effective utilization of relatively less expensive medical manpower. Many residency programs have discovered this in recent years.

I became much more personally sensitized to cost effective measures several years ago while serving as a Commissioner of the North Carolina Medical Society, at which time I was heavily involved with the re-organization of our Society's Committee on Cost Effective Health Care, so ably chaired by Dr. Ira Hardy. One of the simplest things that occurred to me as the Blue Cross/Blue Shield Regional Hospitalization Utilization Data were presented, was to consider our habit of preadmitting patients for major open heart surgery *two days* in advance of the scheduled surgical date. A little over a year ago we shortened our preoperative in-patient stay by one day for cardiac surgical patients. Whereas we formerly brought a patient in two days before surgery so that intensive preoperative laboratory testing and in-depth orientation by physical therapy, inhalation therapy, ICU nursing staff, and others could be provided, we now do much of this on a pre-admission basis and all of it is accomplished within twenty-four hours of surgery. At the time our open heart surgery case load passed three hundred we implemented this shorter hospital stay and have effected considerable cost savings. This simple step has saved over three hundred in-patient days in the past year alone.

Another new program that I have observed in this community has been the establishment of an ambulatory intravenous drug program. This has been extremely successful. Patients who formerly remained in the hospital for anywhere from four to six weeks for intravenous antibiotic therapy associated with endocarditis or valvulitis can now go home many weeks ahead of time and be followed either by our group or the cardiology group and our infectious disease colleagues. It not only has saved money, it has made the patient's lifestyle much more pleasant and tolerable in many instances.

Now, at the risk of being on the receiving end of considerable heat, I would point out one other evolving practice pattern that has disturbed me for years. This is a pattern that exists in communities in the state that usually have a relative doctor surplus, and fortunately it is not a major problem in Asheville. This is a pattern wherein the patient's primary care physician (used in a generic sense) makes an appropriate diagnosis on an ambulatory basis that clearly calls for a standard surgical intervention. That patient is usually seen by the surgeon but lo and behold is then admitted by the referring physician, has a complete comprehensive hospital "workup" and is seen daily preoperatively and postoperatively usually up to the time of discharge by one or more internists, family practitioners, etc. I can understand this in patients who have impaired reserves involving different organ systems. It then becomes a medical necessity and a wise and prudent involvement of associates. However, I do feel that specialists in surgery should be able to admit a patient on their own, do a competent medical workup, operate on that patient and take care of the usual and common postoperative problems without having to get into what I call practicing medicine by committee. There is no question that the patient today benefits substantially from the input of expert consultants from a variety of fields when that patient has multisystem dysfunction. However, all of us need to *learn* some of the care

principles that our consultants in infectious disease, pulmonary medicine, cardiology, nephrology, endocrinology and other specialized fields teach us as they work in a collaborative relationship. A heightened sense of what this means in terms of cost came home to me in a personal way after my father was hospitalized for major pulmonary surgery. He developed postoperative complications and I am eternally grateful for the care he received by a team of physicians which included a cardiologist, a pulmonary medicine specialist, a nephrologist, and my own surgical colleagues. However, it became quite obvious that twice a day visits to the Intensive Care Unit, while appropriate and very much appreciated, can and do result in substantial increases in professional fees to the individual patient. I think it behooves all of us to be aware of this and to convene multiple disciplinary M.D. care teams when it is truly indicated.

Finally, I would point out that recently we have seen a number of "grocery lists" of so-called "approved" ambulatory surgical and diagnostic procedures that have come from a variety of reimbursement groups. It is quite conceivable for a physician to go through a complete Certificate of Need, build an ambulatory surgical center, apply for and get a license and then start to do innovative and new ambulatory surgical procedures and not be reimbursed by Medicare or Medicaid in his/her surgicenter simply because the procedures that the physician decides can be done less expensively are not on the Federal Registry approved schedule. Likewise, a number of Blues and other commercial carriers have sent out sample lists of procedures that will not only be paid for on an ambulatory basis, but will be paid for in spades. These lists may leave out other procedures that might indeed be considered for less expensive ambulatory care. Thus, I continue to have a major frustration with those evangelistic cost containment proponents in that they complain about the problems and at the same time throw up enormous bureaucratic obstacles to innovative approaches on the part of physicians. Why not let physicians and surgeons decide for their patients what can be done safely, efficiently, and in a cost effective fashion outside the hospital and then reimburse that physician fairly for his innovative care?

From Dr. Jacqueline Pugh, a fellow in internal medicine in Durham.

Residents in a private hospital often feel as if they have little control of spending on the private patients for whom they care. Each of my three years here at Duke revealed to me ways in which I directly added to costs or, conversely, contributed to significant savings:

seeing chronically ill clinic patients frequently and regularly in an effort to prevent frequent emergency room visits and hospitalizations;

working closely with visiting home nurses and physical therapists to identify new or worsening problems before they require hospitalization;

never ordering "routine" admission studies but instead ordering only those tests necessary to diagnosis or management of that particular patient;

spending an extra hour or two on the telephone to schedule diagnostic tests prior to admitting a patient so no time in the hospitalization is wasted;

providing work and home phone numbers to my sickest clinic patients to try to decrease emergency room visits;

using the telephone to track down previous study results on referred patients thereby cutting down on repetition;

discussing patient progress with nurses, respiratory therapists, physical therapists, etc. in an effort to tailor care effectively to the individual patient;

filling out funding and placement forms speedily.

From Dr. John Stratton, an internist in Durham.

I believe the medical profession in general has not "come to grips" adequately with medical costs; there is much talk about cost containment, but little changes from year to year. I suggest some principles from the perspective of a primary care internist. I know what I do; I cannot be certain what is *effective,* since I cannot document *my* costs and outcomes.

1. The first requirement is a change in attitude. We must believe that costs really are very high for most patients. We must believe we can influence those costs, and try daily to limit costs.

2. More medical judgments are required as to what is *really* needed. A classic tool of medical education is the differential diagnosis. Too often we conclude our responsibility is to "rule-out" everything on the differential. Its purpose is for our *thinking;* but then we must make careful choices as to what we really think is wrong, what tests are most important, and what will influence our management.

3. Medical care should be viewed as continuing through time. A remarkable number of complaints resolve with time. It is easy to justify many tests to define the basis of symptoms, but we have no obligation to resolve all problems *now*. Over and over I tell patients I don't know what is wrong, but they are not seriously ill *now;* I will reevaluate the symptom next week, or next month; certain tests are indicated if the symptom persists; and meanwhile I'm available if the situation changes. This clearly involves risks, and living with uncertainty, but it is also based on training, knowledge, and experience.

4. In-patient and out-patient care should be a continuum. I regularly take some of a patient's office record to the hospital to document past problems and tests, and this may bypass some repeat tests. I often complete some tests as an out-patient that could easily have justified another day or two in the hospital.

5. Our profession *and* our culture must give special attention to medical decision making for very elderly patients. We doctors do too many tests, operations and treatments on debilitated patients that do not contribute to meaningful life. I am convinced that most patients and families are willing to discuss this and are willing to consider *not* doing what might be easily justified.

6. We need additional concern about medications. Some patients spend amazing amounts on medicines. I regularly review all medicines and plead with patients to bring them regularly. Often there are cheaper alternatives, doses and frequencies can be reduced, some medicines can be stopped, P.R.N. medicines are used excessively, and there

are often non-medication alternatives.

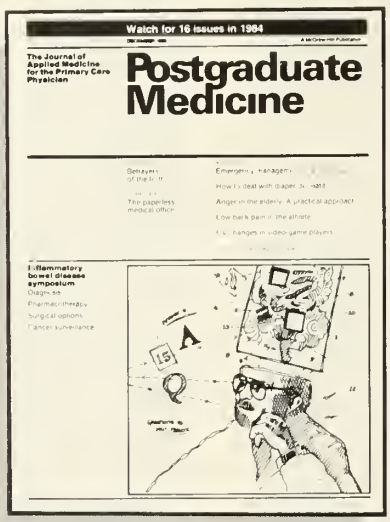
7. Doctors need to work harder on lifestyle changes — inactivity, obesity, smoking, tension, etc. Indeed, it is frustrating and the results are poor, but I believe it is essential if we are serious about reducing costs. Respiratory complaints are remarkably reduced without smoke; I have stopped many blood pressure and diabetic medicines after a modest diet and weight change.

• EDITOR'S NOTE: These opinions suggest to me that there are at least four ingredients for successful cost-containment strategies: an appropriate attitude to appreciate the need to contain costs; the common sense to think of useful changes in diagnostic and therapeutic strategies; an ability to make decisions under conditions of uncertainty; and the existence of proper financial incentives. I know from my experience at a university hospital that strategies to teach cost-effective health care have very little impact if any of the ingredients are missing. We would appreciate hearing any comments from our readers on this important subject.

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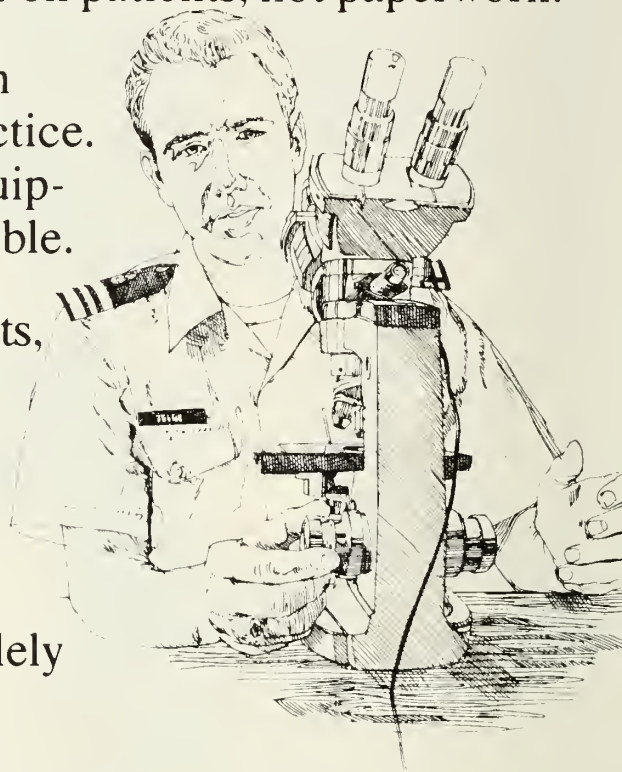
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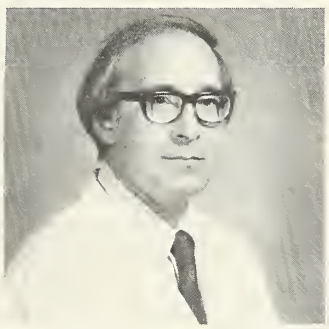
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The Duke Cabarrus Medical Education Program*



Galen S. Wagner, M.D.



Thomas T. Long, M.D.

It is desirable to have continuing mutually beneficial interaction between physicians in practice and those in the academic medical centers who are responsible for training new physicians. As capable physicians complete training and move into adjacent communities, the patterns of patient referral to the academic medical center change, often resulting in a change of the patient population available for house-staff training. Likewise, diminishing federal funds are influencing programs to alter patterns of training. Supplemental programs for house-staff training would be helpful, particularly if they expose the trainees to patient populations not regularly seen, and if they simultaneously provide additional funding for the medical center.

Physicians in private practice are continually challenged to upgrade their diagnostic and therapeutic skills because of the rapid development of new technologies. Effective continuing educational programs are needed. Ideally these programs should not require travel or time lost from practice. As the practitioners gain new skills and knowledge, earning power increases. A portion of these earnings could be returned to the academic medical center to support the training of new physicians in return for the establishment of a continuing educational program in the community utilizing senior trainees and faculty.

This report describes a successful educational relationship between an academic medical center and a local community hospital. The Duke/Cabarrus Medical Education Program, over the eleven years of its existence, has had an important impact on the trainees, the medical center, the practicing physicians, and the community hospital.

In the early 1970s when the general physicians in the community hospital in Cabarrus County had determined their need for additional continuing medical education, they decided to establish an educational affiliation with the Duke University Medical Center.

The situation had several unique elements. 1) Many of the Cabarrus County physicians had been products of the Duke University Medical Center. 2) Eugene A. Stead, Jr., who had voluntarily retired from Chairmanship of the Department of Medicine in 1968, was available to turn his attention outside the doors of the academic medical center toward the development of other programs. 3) The Cannon Foundation, which had traditionally supported Cabarrus Memorial Hospital and the provision of high quality, cost effective health care, had also expressed a desire to develop an effective continuing medical education program. The Cabarrus physicians used Dr. Stead's time to help develop a program that would use the resources of the Cannon Foundation to create an educational affiliation which began in 1973 and which has survived and grown through all the changes of the academic medical center-community hospital relationships until the present.

The academic medical center needed funds to train subspecialty fellows, the fellows needed a workshop in the community hospital to develop their consultative skills, and the general physicians in the community hospital needed the on-the-job training these subspecialty fellows could provide them. Beginning in July 1973, fellows from five of the divisions of internal medicine began to travel for two 48-hour periods per month to function as educational consultants to the general internists at Cabarrus Memorial Hospital. In return for having a consultant present for one

* The authors wish to acknowledge the assistance of Ladd W. Hamrick, M.D., Robert L. Wall, Betty C. Steele, R.N., and S. Spence McCachren, M.D., in preparing this report; and Sandra Gilmore and Gail McKinnis in preparing the manuscript.

24-hour period per week, the community hospital, through funds provided by the Cannon Foundation, supported the entire stipend for that fellow's training. Dr. Stead had advised that education programs between academic medical centers and community hospitals more often failed than succeeded because the academic centers did not require sufficient funding for these programs. He felt that the academic medical center would only be interested in continuing this program over time if the amount of money received were sufficient to compete with other potentially available funding sources. Physician scientists in the leadership roles in the academic medical center would only support the community hospital educational affiliation by providing the time of their fellows if, as in the novel *The Godfather,* "there was an offer they couldn't refuse."

Over the twelve years of its existence, the educational affiliation between Cabarrus Memorial Hospital and Duke University Medical Center has grown in many ways. Though this report relates only to the program in internal medicine, there were also programs in general and thoracic surgery, urology, orthopedics, otolaryngology, obstetrics and gynecology, and pediatrics, which continue to the present. Programs subsequently developed in pathology, psychiatry, and radiology. The community physicians are now matching the contributions of the Cannon Foundation and thus contributing their own generous financial support to the program. A unique aspect of the program is that the educational consultations are provided with no charges to the patients. Cabarrus Memorial Hospital has become the site of one of the regular senior assistant residency rotations in internal medicine. New and excellent generalists and specialists have moved into the community, many because of the existence of the educational affiliation.

Two full-time members of the Duke University Department of Medicine are based in the community to coordinate the activities of the residents and fellows. An additional full-time faculty member based at Duke travels one day per week to the community to assist in this coordination. The program is administered through the full-time activities of a former Director of Nursing In-service Education and her secretary at Cabarrus Memorial Hospital and the part-time activities of a staff assistant of the physician coordinator at Duke. As of July 1984, one fellow in each of the ten divisions of internal medicine at Duke is fully financially supported by educational consultative activities at Cabarrus Memorial Hospital.

The program at Cabarrus Memorial Hospital has served as a model for the development of educational affiliations between the Duke University Medical Center and ten other community hospitals in North Carolina and southern Virginia. North Carolina has participated in the Area Health Education Center (AHEC) program since the mid-1970s and this source has provided the primary funding for initiation of these other programs. The academic medical center realized that flexibility would be required both in the identification of funding sources and in program design in each community. After the medical center presented its concepts for these programs to the individual communities, time was required for sufficient barriers to be cleared so that the programs might be successfully implemented. Though the Cabarrus program was the model, other programs were not judged on their ability to duplicate that model but rather on their ability to fit comfortably within the context of that particular community's physicians and that particular community hospital.

Several reports in this issue of the *North Carolina Medical Journal* have originated from one of these community hospital programs spawned by this Cabarrus model. The Henderson program is different because it exists in a different medical community.

During the 1980s the survival ability of both the academic medical centers and the community hospitals will be challenged, primarily by the emergence of a hybrid institution: the large non-academic medical center with commitments to 1) as much general care as the traditional community hospital, 2) as much specialty care as the academic medical center, but 3) not as much academic activity in either research or education as the traditional academic medical center. These centers aspire to be all things to health care needs. However, they will produce a sterile medical society, because the physicians practicing in these institutions will be unable to either reproduce themselves or produce the knowledge required to determine the effects of the techniques they administer to their patients. Therefore, physicians practicing in these multifaceted medical centers have as great a stake in the success of the educational affiliations between the academic medical centers and the traditional community hospitals described in this report as do the physicians in these two differing but dependent institutions. Perhaps the reports in this issue of the *Journal* may serve to present the model of the Cabarrus program to the wider scope of the medical community and, thereby, to stimulate the question, "What can each of us do to assure the vitality of medical practice for the future?"

The Duke/Henderson Medical Education Program

Thomas A. Reichert, M.D.

In the state of nature, most successful organisms, both social and biological, exhibit territorial behavior. They succeed because they identify and defend territory in which they define a niche, a special role in the social/biological strata. In harmonious societies, aggressive behavior is at a minimum with most social and biological forces poised in postures which pressure all of the elements of the society back toward harmony and stability. In the 1930s, a theory arose to describe optimal behavior in competitive situations. Called A Theory of Games and Economic Behavior, this theory has been widely adopted in international political, in corporate, and even in interpersonal strategies. A fundamental result of this theory is that the strategy which produces a situation in which all parties have some power achieves the most peaceful and successful results. All parties gain most by cooperating. When aggressive behavior is initiated by any party, the most effective strategy is for all other parties to direct retribution against that individual, inhibiting his behavior and restoring harmony.

In the evolution of social systems, a cycle begins with the

development of individuals with the capability and strength to interact with their immediate environment. This interaction ultimately brings them into contact with other individuals. Their initial interactions are usually aggressively competitive; and it is only after a period of negative reward that most systems settle into a pattern of cooperation. The pattern of growth of hospitals and medical centers in the United States has usually been one of a gradual development of individual institutions in relative isolation. Interaction has usually been at a distance with a clear division either in territory (in the case of institutions of equal facility) or in level of care (primary versus secondary/tertiary). The recent sharp rise in numbers of physicians has led to a wider availability of subspecialty skills and a concomitant increase in the quality and capability of hospitals in smaller communities. Some of the competition which has grown out of this strengthening has been aggressive and territorial. Less frequently, hospitals have joined together to seek, in cooperation, a union greater than its parts.

In this issue of the *Journal,* we will present a sort of testimony from a number of participants in a rather remarkable experiment. AHEC, Duke University Medical Center in Durham, North Carolina and Maria Parham Hospital in the town of Henderson some 40 miles away undertook an exercise in cooperation which began seven years ago. In the report of the Duke/Cabarrus program, Wagner and Long place in historical perspective some of the pressures that led the medical center to extend its resources into programs designed to be molded to the needs of neighboring communities. Millard Wester, M.D. has been the principal architect of the connection fashioned at the community level in the Henderson program. He describes for us the evolution of that interface as seen from the community's viewpoint. Our central theme is a portrayal of the attitudes and preconceptions that came to this project together with their evolutionary changes when both institutional parties learned the ways in which the various needs were served.

The mechanism used for medical center extension is a program where physicians in the late stages of their training in subspecialties of internal medicine provide consultation and other related resources in a community hospital where subspecialties of internal medicine are represented by only a very few practitioners. Through the traditional mechanism of case presentation, we will follow two patients as their medical conditions were recognized by their personal physicians and were shared with the consultant. As care needs exceeded those locally available, a program of augmented care was fashioned. In the first case the patient required physical transfer to the medical center where diagnostic and surgical facility not available in the community could be provided on an emergent basis. In the second case, a program of augmented care could be constructed and implemented at the community level. Medical center level expertise not economically plausible within the community because of limited need could, nevertheless, be made available on a limited basis sufficient to guide the personal physician in constructing an appropriate program. Each of the contributors has tried to present aspects of discovery and learning which this program of cooperation provided to them personally. Both patients and physicians have been asked to be as candid as possible.



Millard W. Wester, Jr., M.D., Henderson Coordinator, Henderson Outreach Program

There has long been a misconception that there are significant differences in medical opinion, practice and policy, and that a low level of cooperation is the natural relationship between "town and gown." In the belief that the end result of cooperation is likely to be better patient care, more efficiently delivered at a cheaper cost, a unique challenge arose to the "old folks" tale. A cooperative project designed to interweave the patterns of care at Maria Parham Hospital in Henderson and Duke University Medical Center in Durham was conceived in conversation in May of 1975 and put into practice in 1976. The initial concept was to create an extern program within Maria Parham Hospital. After discussion of many alternatives, we settled upon a resident consultant program in which a resident in medicine at Duke would visit our community, discuss referrals with doctors, interview and examine patients and then return to the medical center where he would consult with the senior staff members in the specialties that presented themselves in the patient's problems. The resident would then communicate back to the referring physicians either in person or by phone with suggestions for care and therapy. Senior staff members would also visit Maria Parham Hospital from time to time to more fully evaluate the course of the consultations and therapy.

Such a program was instituted in 1976; but after one year in that mode, the program was altered to better suit our needs. This alteration included the substitution of a number of fellows in several subspecialties of internal medicine. Cardiology, rheumatology, neurology, endocrinology, hematology, rheumatic diseases, and infectious diseases were originally included on a rotating basis. Because of the increased experience of the fellows, consultations could usually be accomplished and therapy outlined within the local hospital setting. Frequently, tests performed at the local hospital resolved a diagnostic dilemma without the patient having to leave our community.

Another bonus has been having a physician available who is familiar with the system at Duke Medical Center to help us make referrals and/or arrangements for studies expeditiously. With time and experience, we have found ourselves making outpatient referrals for studies that in the past required hospitalization, such as exercise tolerance tests, CAT scans and EEGs.

We are presently operating under this system with patients seen both as outpatients and as hospital inpatients. Pre-consultation information is supplied by the local doctor; and after seeing the patient, a person-to-person discussion is usually arranged between consultant and personal physician at which time diagnostic and therapeutic options are discussed. If emergent care or care exceeding local resources is required, transfer arrangements are made

with the efficiency that only insiders can evoke. An added bonus to transferred patients is that they already have a Duke physician with whom they are familiar who will follow up their care when they arrive at Duke Hospital, report their progress and arrange their transfer back to local care.

Positive benefits of our program fall into three major areas: those to the patient, to the physicians at Maria Parham, and to the physicians at Duke.

Patient benefits derive from the faster, more efficient diagnosis and access to newer alternatives to traditional therapy. For example, in the field of cardiology, Maria Parham Hospital has not had to "gear up" to tests that could not be cost effectively utilized locally, including radionuclide scanning, cardiac catheterization and pacemaker placement. In a sense, our hospital becomes an extension of Duke's facilities for efficient utilization of these particular tests. Patients no longer need be admitted to Duke Hospital for evaluation prior to testing, but rather can be sent to the medical center only for the time period required for the testing or therapy.

Another positive effect on patient care is that a program of augmented care can often be created within the local community setting. This increase in level of care comes at a considerable saving both in the reduced cost of local hospital room and service charges and in the peripheral cost of transportation and family visitation to the more remote medical center.

Expeditious handling of emergencies with the help of the consultant physicians quickly replaces less effective referral mechanisms; and same day referral for non-emergent care has frequently been the rule. By comparison, there is usually a one or two week delay in scheduling admissions or even outpatient examinations, tests, or therapy for patients entered outside the consultant program.

Local physicians have also benefited in that their learning process for each patient has been expanded by the input from the consultant. The consultants have conducted a "Breakfast Club meeting" every other Tuesday morning at which time they spend one hour on some aspect of medical diagnostic care or disease processes. This small group setting has allowed for considerable dialogue and "honing in" on the areas of mystery or concern in some of our more common problems. The consultant physicians are also a resource for evaluation of hospital policies and practices. An excellent example is the input that our infectious disease consultant provided in aiding us to establish an effective program of infection control (see the article by Dr. Clark Kerr which follows). Policy has been re-examined in many of our patient care areas based on input from the consultant physicians with a savings that would be difficult to estimate.

To the fellows and physicians who have come to Maria Parham Hospital from Duke Medical Center, I would adjudge a positive benefit simply being that of first hand contact with the private practice of medicine. We have been pleased at the growing awareness that a high level of medical care can be delivered in such a community.

A new aspect of medical care that is being explored through this system is that of reverse referral. Patient care begun at the local hospital is occasionally complicated by a need for tests and/or therapy unavailable in the community. After transfer to the medical center for the acute need, the patient is referred in reverse back to Maria Parham Hospital as soon as stabilization permits resumption of local care. This mutual "vote of confidence" is not only good public relations for both hospitals but also efficiently utilizes the resources of both care centers, minimizing costs.

It is difficult to challenge aphorisms and "old folks" tales. This program has been a delightful opportunity to increase the cooperation of the local physician with the academic doctor. We have been particularly pleased with the early results of our program and feel that, with modification as appropriate to each local setting, this will become an important addition to the accepted way of delivering medical care. There have been rough spots, but the good has been real, the positive results have been many and all have been oriented to providing the best care for patients, which is after all the ultimate goal of any physician.



Thomas A. Reichert, M.D., Ph.D., Duke Coordinator, Henderson Outreach Program

The other contributors to this collection will stress the benefits which accrue to the patients and the physicians who care for them, both community and medical center based; but a cooperative outreach program has two additional entities as parties to the interaction. These are the two cooperating institutions; and like all parties to all other social and biological systems, the administrations of such institutions must clearly see mechanisms of benefit in such enterprises if their cooperation is to be whole-hearted and continuing. In July of 1981, I was offered the opportunity to coordinate the Henderson Outreach Program as an adjunct to my staff position at the medical center. Fresh from my own rewarding personal experience as a fellow in the program, I enthusiastically embraced the opportunity. Certain that the obvious benefits derived by patients and participating physicians were easily perceived by the administrations of both hospitals, I approached them individually only to find neither hospital's administration fully aware of the scope of the program and not entirely convinced of its benefits.

In the absence of a line of communication, any institution is inclined to a defensive outlook. The staff of the consultants' program, in concert with the physician community in Henderson, responded by providing nearly complete information on all consultations seen at Maria Parham Hospital and transfers to Duke Medical Center over the subsequent year. Based on admittedly sketchy data from preceding years, we found the rate of increase of consultations to be about 60% per year rising from 70 patients seen the entire first year of operation to 688 patients in the year 81-82. In this year, 600 of the 688 consultations were

formal, leading to notes transcribed to the patient's chart; and 540 consultations involved direct patient contact as opposed to review of patient-related material. Three hundred of the 540 patients (56%) were outpatients seen through the emergency room and the remainder were seen as inpatients. Only 80 patients were actually transferred to the medical center for admission. Approximately two-thirds of these were inpatients at the time of their initial consultations. Thus, only about one consultation in seven actually led to a program of augmented care requiring transfer. All others could be managed locally.

The medical aspects were easiest to assay. Of the first 25 patients transferred to the medical center in that year, five became the subject for grand rounds either in general medicine or in a subspecialty conference. Because these patients were very ill, their length of stay exceeded one week; and their medical bills were correspondingly high. Nevertheless, the overall level of fiscal responsibility was demonstrated to be sufficient so that the consultants' program could operate unfettered by any need for financial screening.

At Maria Parham, we discovered that at least one-third of all consultations referenced the Neurology subspecialty, a fact previously unanticipated. Cardiology, with two consultants available, made up approximately another third of the consultation requests. Thus, as Maria Parham Hospital sought to enlarge its cadre of internists, the scope of their recruitment was broadened to include internists with either cardiology or neurology specialty training.

In addition to physician subspecialty utilization, the specific tests for which patients were referred to the medical center became available to both the administrations. Given the frequencies of referral, a cost effective approach to the acquisition of new laboratory equipment could be undertaken. Medical center consultation was made available in both evaluating new physician prospects and acquiring new equipment.

Finally, it was realized that no formal mechanism existed for coordinating and regulating the flow of patients in referral both to the medical center and, in reverse, to the community hospital. Administrative experiences at both institutions had never been organized so that a review of patient transfers could easily be made. A semi-formal mechanism has now been installed to record and assess the financial resources and medical requirements of each patient transferred between the two institutions. This history will provide a basis for future agreements. Approximately 90% of the referrals from the county surrounding Maria Parham Hospital to Duke Hospital still occur outside the Henderson Outreach Program. For these patients, no mechanism is currently available for coordinating local care and medical center care, which are thereby independent and sometimes conflicting.

The Henderson Outreach Program is a stable and viable enterprise. Each of the five participating entities — two hospitals, two sets of physicians and their patients — have come to see clear benefits to be derived from cooperation. Progress has been real, though we have often had to feel our way. There can be no doubt, however, that in the Henderson Outreach Program indifference and defensiveness have yielded to the nurture of the cooperative spirit.



Clark M. Kerr, M.D., Infectious Disease Consultant, Henderson Outreach Program.

Through the outreach program from Duke University Medical Center to the community hospital, Maria Parham in Henderson, I had the opportunity to visit one day every two weeks for the year July 1982 to July 1983. Initially, my only duty was to be available for consultation and clinical referrals, specifically in the subspecialty of infectious disease and, more generally, in internal medicine. While consultation remained a prominent part of my contribution at Maria Parham, it was in another role that I feel that the community was helped the most and was, in turn, most helpful and stimulating to my own training. This was the role I played on the hospital Infection Control Committee and, at times, on the hospital Pharmaceutical Committee. Shortly before my year began at Maria Parham, an accreditation review had cited several specific lacks in the protocol procedures for infection control at the institution. Working closely with the newly hired infection control nurse, we set about defining protocols for multiple areas relating to infection control within the hospital and the control of infectious disease more generally in the community. Some of the entities covered were 1) isolation procedures for infected post-surgical patients; 2) specification and clarification of isolation procedures for wound precautions; 3) dispensation rules for assigning placements within the hospital for patients with specific diagnoses; for example, adult versus pediatric wards, medical versus surgical wards, contaminated versus non-contaminated areas; 4) distinguishing colonization from infection. Sputum, tracheal aspirates and urinary tract infections were covered in detail.

At the time of my arrival, the staff at Maria Parham had identified the problem that their nosocomial infection rate appeared inordinately high. Upon investigating, I realized that it was primarily a lack of appropriate definition in protocols for infection control that caused the reported infection rate to be so high. Most cases of what was labeled infection and recorded as such in the hospital record were merely colonization. With understanding of the distinction between infection and colonization, new definitions could be applied and appropriate management procedures instituted. Subsequently, the nosocomial rate dropped dramatically at Maria Parham.

Other topics were taken up by the hospital Pharmaceutical Committee. These included the appropriate use of antibiotics, acceptable combinations of antibiotics, surgical prophylaxis with antibiotics, and recommendations for hospital formulary inventory of late generation antibiotic agents together with suggested restrictions for their use. These last issues had only just come under scrutiny at the time of my leaving Maria Parham and Duke University. We saw a large part of our mission as that of defining those areas of primary importance.

It was, I feel, a successful year both for myself and for the hospital. The hard evidence is the national board review which issued *no* citations this year at Maria Parham for standards of infection control and generally expressed delight with the progress made in the two years since the last review. I will be following with keen interest the reports of my successor in the consultant's role in infectious disease at Maria Parham.

Millard W. Wester, Jr., M.D., Practitioner, Family Medicine, Henderson, NC

Since returning to Henderson, North Carolina in 1953, I have furnished medical care and advice for my friend and neighbor, Mr. Charles Blackburn. Indeed, we have been friends since early childhood. I, therefore, have had the opportunity to see him for early phases of problems and to control and/or prevent difficulties before they reached severe proportions.

As early as 1965, Mr. Blackburn began to have episodic respiratory difficulty characterized occasionally by sputum production and, more recently, by bronchospastic wheezing. On most occasions he responded to the usual medication for "colds" including antihistamines and, occasionally, decongestants. On some occasions, antibiotics were prescribed because of changes in physical examination and/or laboratory findings as well as sputum changes. In 1980, he had an episode of bronchospastic wheezing severe enough to require prednisone treatment, the taper of which was most effective. It was noted since that time that he in fact responded rather poorly to antibiotics, but rather dramatically to prednisone taper doses. In April of 1983, he had two episodes rather dramatically difficult to control except with prednisone. Because these occurred so close together, I suggested that we have a consultation. Mr. Blackburn had already received good advice through the consultative services with the Duke consultant rheumatologist in the Henderson Outreach Program relative to controlling some of his arthritic symptoms. We quickly and mutually agreed that the pulmonary consultant in a local setting would be an excellent source for further information. As detailed in Dr. Bishop's report and in Mr. Blackburn's summary, we were able to elicit not only the reasons for his paradoxical responses to medication but, with further input, were able to shape a program which has been most successful in controlling almost completely this gentleman's difficulty to date. I am convinced that had we not had the availability of a consultant in the local setting providing expert information and advice without requiring the patient to give up so much of his professional time away from the office, we would have had difficulty persuading Mr. Blackburn to let us obtain a second opinion, and thereby alter the therapy so dramatically for his good response. In short, I think that this exemplifies the opportunity to conveniently access and treat early for the patient's better care in a most cost- and time-effective manner.



Clark Bishop, M.D., Pulmonary Disease Consultant, Henderson Outreach Program

I was asked to see Mr. Charles Blackburn in April 1983. He had been having episodes of sputum production accompanied by bronchospastic wheezing. He improved following steroid tapers but not after antibiotics. After having had several such episodes, Mr. Blackburn joked that as an attorney, he could not afford to get out of breath. Both he and his family physician, Dr. Millard Wester, were concerned that he might have developed an allergy to something. We had Mr. Blackburn come in for allergy testing and for pulmonary function tests. These studies revealed unimpressive allergic reactions to skin test antigens. Pulmonary function tests showed FEV 25-75 decreased to 41% of predicted values, suggestive of small airway obstruction. I discussed these results with Mr. Blackburn and Dr. Wester. Since the chances of improvement with immunotherapy were small we decided not to follow that avenue. We felt that he could get the benefit of steroid therapy using inhaled beclomethasone and we could avoid the systemic side effects of prednisone. It was then that Dr. Wester recalled that while Mr. Blackburn's alcohol intake was moderate, he nevertheless seemed worse after having a few drinks. We then devised a program of bronchodilator therapy, inhaled beclomethasone and steroid tapers only when necessary for exacerbations, as well as strict avoidance of alcohol. Mr. Blackburn has done very well on this regimen.

This case illustrates a blending of the art and science of medicine in a cooperative interaction between the referral hospital and the community physician. At the referral hospital we were able to provide data to suggest which methods of therapy would likely be helpful. Dr. Wester, the family physician, was able to discern nuances about Mr. Blackburn's case and made suggestions to optimize the care. Furthermore, Mr. Blackburn did not require hospitalization at the referral center and lost minimal time away from his law practice.

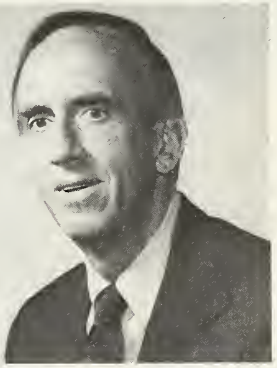


Charles F. Blackburn, Patient, Henderson Outreach Program

After examining me, Dr. Wester suggested I see the specialist from Duke. He set up an appointment, and when I went over to the local hospital to see him, I didn't have to wait. I went right on through. The Duke consultant performed some tests and evaluated them. Then he and Dr. Wester consulted about my case and prescribed what I should do.

First of all, it was a great convenience. I didn't have to go to Durham. Everything was done right here. The fee was incredibly low. I think it was $50. The fact that the specialist from Duke comes here seems to give him more time to consider each individual case, and the patient feels he's getting more personalized care. Plus, it's less physically demanding on the patient. I didn't have to go to Durham and worry about a place to park or worry about navigating through the medical center. Instead, I received expert care in familiar surroundings, just a few minutes from home.

Our second case illustrates how a cooperative interinstitutional system can be harnessed with speed and dispatch when an emergent condition arises. Our contributors, the interacting local personal physician and the outreach consultant, develop here insight into the specific changes the interrelationship has made in this aspect of the delivery of medical care in the community.



G. Reginald Tucker, Jr., M.D., Practitioner, Family Medicine, Henderson

In spite of modern transportation and communication, a primary physician in a small community can feel medically lonely and isolated in situations where diagnosis may be confusing and unclear. When such a situation arises in a crisis setting with a need for rapid evaluation and therapy, access to a large medical center can be very comforting. Just such a situation occurred recently when a young woman in generally good health was seen two weeks to the day after she had suffered a physical beating. She had been evaluated shortly following the incident and no serious consequences of her abuse seemed evident. She was re-evaluated several days later and then returned to her work as a skilled typist. Yet, on the day of the crisis she was brought in at our direction, drowsy, and with a headache, but coherent, oriented, and able to walk. There were only soft, suggestive neurological signs; but our exam raised serious suspicions. A call to the neurological consultant in the Henderson Outreach Program and a brief expression of our concern led to a rapid ambulance transfer directly from our office to the Duke Emergency Room where superb handling and rapid CT scanning confirmed the presence of a subdural hematoma of large size threatening tentorial herniation. Immediate neurosurgical intervention with burr holes and craniotomy resulted in a remarkable recovery.

The consultant program contributed to this successful outcome in several ways. The consultant was *known* to the physician and rapid direct contact was possible leading to smoother logistical handling of the case. The physician was *known* to the consultant who could thus more readily appreciate the concern and the evaluation presented. Having worked in the community, the consultant *understood* what technical facilities were (or were not) available and could also understand the dilemma of the local physician. Finally, the local physician had benefitted from ongoing update and refresher programs provided by the consultants (at Breakfast Club talks and through personal contact in the handling of individual patients), making the recognition of less frequently seen problems more prompt and accurate. It seems that all of the attributes of the consultants program were at work here and provided an immeasurable benefit to all concerned.



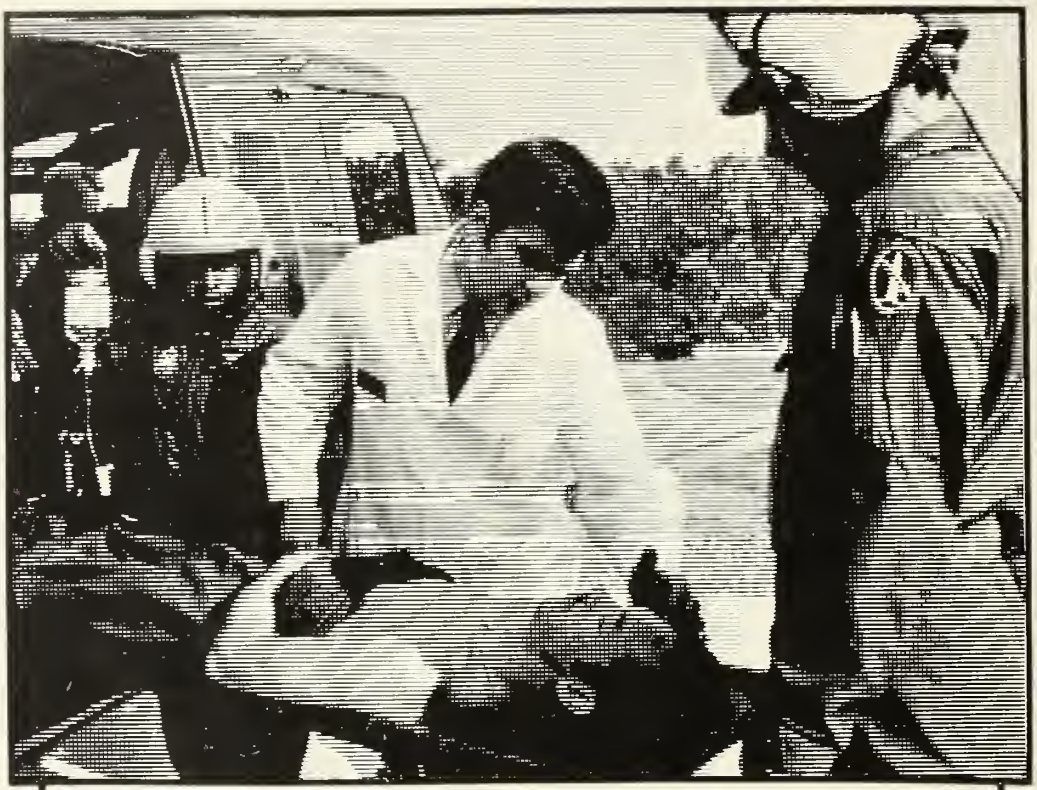
Virginia Pact, M.D., Neurology Consultant, Henderson Outreach Program

In September 1983, I received a call from Dr. Tucker in Henderson concerning a patient who had suffered head trauma two weeks previously. This young woman worked as a legal secretary and was a personal friend of the referring physician. She had been the victim of family violence and although she was still working, she complained of a very severe headache. Her headache had worsened in the last few days, and on the day I was contacted, she had not been able to go to work. Her physician called her at home and was concerned because she seemed so lethargic. He persuaded her to come to the office. She was indeed lethargic, but without focal findings. He felt she needed an emergency CT scan to rule out a subdural hematoma.

The patient was immediately transferred to the Duke Emergency Room for further evaluation. The neurology resident found her to be lethargic, but in addition noted that she had difficulty with eye movements and had left arm and leg weakness. Because of the lethargy and rapidly evolving focal signs, a CT scan was obtained emergently which showed a large left-sided acute and subacute subdural hematoma. The clot was evacuated by the neurosurgeons the same evening and the patient has done extremely well since then. (In passing, it is interesting to note this was a *left* subdural with *left* body weakness — an example of compression of the contralateral brainstem against the edge of the tentorium — the so-called Kernohan's notch.)

The successful outcome in this patient's case began with the recognition of the seriousness of her condition by her family physician. The development of the Duke outreach program has made it easier for the community physicians to contact the appropriate doctor, speak to him or her personally, and by that means arrange for specialist evaluation. This is particularly important in an emergency situation and indeed, proved life-saving in this patient's case.

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IN STATE

September 21

Sixth Annual Health Law Forum
Place: Greenville
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200.

September 21-22

New Advances in the Treatment of Sickle Cell Disease
Place: Wrightsville Beach
Credit: 8 hours Category I
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878.

September 28-29

Adolescent Health Issues: Challenges for the 1980s
Place: Durham
Credit: 9 hours Category I
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878.

October 1-5

Nuclear Magnetic Resonance for the Imaging Team
Place: Winston-Salem
Credit: 30 hours Category I AMA
Fee: $500
Info: Richard Witcofski, Ph.D., Department of Radiology, Bowman Gray School of Medicine, Winston-Salem 27103.

October 1-5

Microsurgery Workshop
Place: Durham
Credit: 40 hours Category I AMA
Info: Jackie Brooks, Box 3372, Duke University Medical Center, Durham 27710. 919/684-3347

October 3

Practical Solutions for Common Medical Problems
Place: Research Triangle Park
Credit: 6 hours Category I AMA
Info: Kathy Hundley, Educational Services Coordinator, Burroughs Wellcome, Research Triangle Park 27709. 919/248/4904

October 3-4

24th Annual Charlotte Postgraduate Seminar
Place: Charlotte
Credit: 16 prescribed hours AAFP
Info: J. Lewis Sigmon, Jr., M.D., Box 32861, Charlotte 28232. 704/331-3172

October 5-7

Practical Problems in Arthritis Management
Place: Wrightsville Beach
Credit: 9 hours Category I AMA
Fee: $65
Info: NC Chapter of the Arthritis Foundation, Box 2505, Durham 27705. 1/800/672-0949

October 13-14

Radiology Mini-Course in Abdominal Imaging
Place: Durham
Credit: 10 hours Category I AMA
Info: Cindi Easterling, Box 3108, Duke University Medical Center, Durham 27710. 919/684-6878

October 24-27

Fall Seminar, American Academy of Clinical Anesthesiologists
Place: Asheville
Credit: 11 hours Category I AMA
Info: AACA, Knoxville, TN 37919-1691. 615/588-6279

October 26-27

Psychopharmacology: Practical Drug Treatment of Psychiatric Disorders
Place: Chapel Hill
Credit: 10 hours Category I AMA
Fee: $125
Info: Nancy Williams, Department of Psychiatry, UNC School of Medicine, Chapel Hill 27514. 919/966-4738

October 26-27

Advanced Cardiac Life Support Instructors Course
Place: Winston-Salem
Credit: 20 hours Category I AMA and ACEP
Fee: $250
Info: Earl Schwartz, M.D., Emergency Medicine, Bowman Gray School of Medicine, Winston-Salem 27103.

November 1-2

Current Topics in Urology
Place: Chapel Hill
Credit: 13 hours Category I AMA
Fee: $125
Info: Barbara Judd, 428 Burnett-Womack Building 229H, Chapel Hill 27514. 919/966-2571

November 11-14

Advanced Clinical Teaching Skills
Place: Rougemont
Credit: 20 hours Category I AMA and AAFP
Info: Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

December 4

Duke Tuesday
Place: Durham
Credit: 5 hours Category I
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

OUT OF STATE

September 20

Use of Computers in the Medical Office
Place: Johnson City, TN
Credit: 6 hours Category I AMA
Fee: $60
Info: Sue Hutchinson, Quillen-Dishner College of Medicine, Johnson City, TN. 615/928-6426, ext. 204

October 12

Selected Topics in Pediatrics
Place: Norfolk, VA
Info: Jean E. Shelton, M.D., Children's Hospital of the King's Daughters, 800 West Olney Road, Norfolk, VA 23507. 804/628-3798

October 18-25

Review of Clinical Chemistry Seminar
Place: San Diego, CA
Credit: 40 hours Category I AMA
Fee: $315
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

October 20-27

4th Diving Accident and Hyperbaric Oxygen Treatment
Place: Grand Cayman, BWI
Credit: 26 hours Category 1 AMA, AAFP, ACEP
Info: Cindi Easterling, Box 3108, Duke University Medical Center, Durham 27710. 919/684-6878

October 22-26

Postgraduate Course in Diagnostic Imaging
Place: Bermuda
Credit: 25 hours Category 1 AMA
Fee: $495
Info: Jacqueline D. Wright, Box 3808, Duke University Medical Center, Durham 27710. 919/681-2711

November 13

Divorce, Child Custody and the Family
Place: Johnson City, TN
Info: Sue Hutchinson, Quillen-Dishner College of Medicine, Johnson City, TN. 615/928-6426, ext. 204

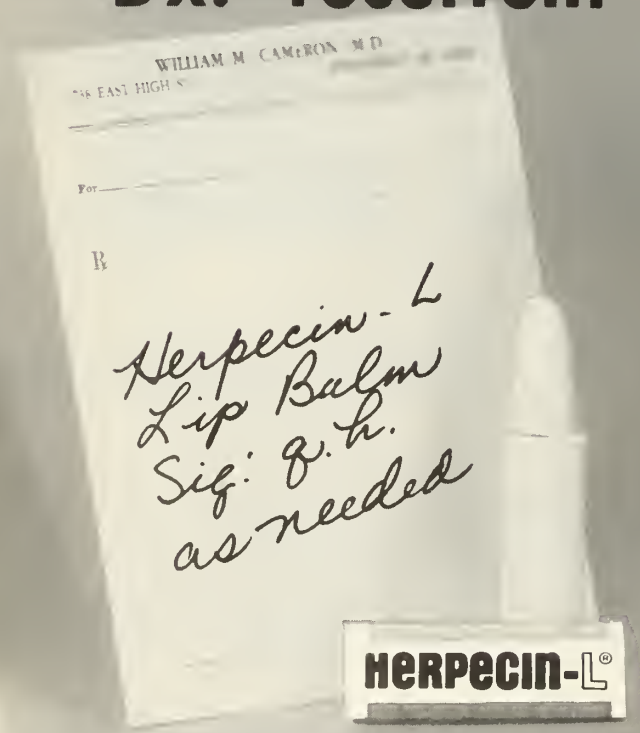
November 14-17

Williamsburg Symposium on Perinatal Care
Place: Williamsburg
Credit: 12 hours Category 1
Fee: $200
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

December 6-15

Review of Clinical Chemistry Seminar
Place: Snowmass, CO
Credit: 40 hours Category I
Fee: $315
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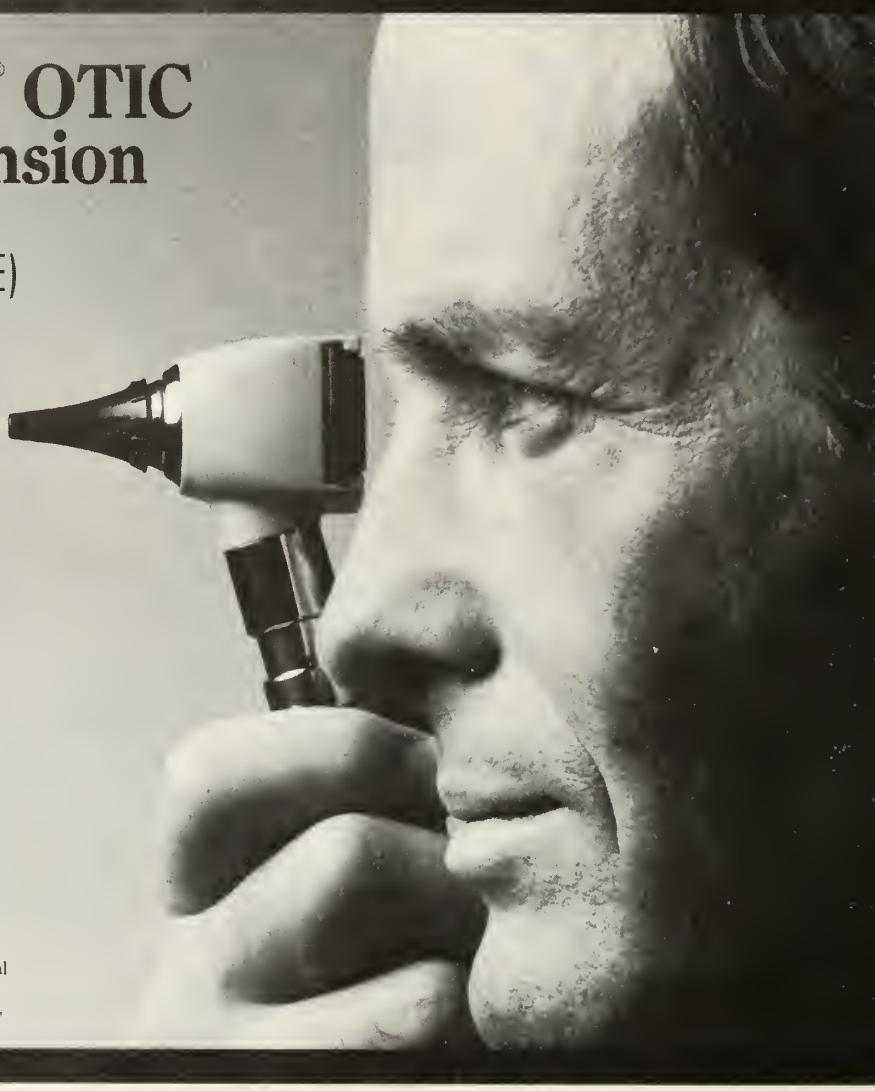
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Responders	91 (97.8%)
Solution	
Total ears	107
Responders	104 (97.2%)
Combined suspension and solution	
Total ears	200
Responders	195 (97.5%)

Adapted from Cassisi et al.[1]

REFERENCE:

1. Cassisi N, Cohn A, Davidson T, et al: Diffuse otitis externa: Clinical and microbiologic findings in the course of a multicenter study on a new otic solution. *Ann Otol Rhinol Laryngol* 86(suppl 39, pt 3):1-16, 1977.



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Warnings: As with other antibiotic preparations, prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

Precautions: If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

Adverse Reactions: Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

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Letters to the Editor

Anaphylaxis from Insect Stings

To the Editor:

There have been reports of unexplained deaths in healthy teenagers following exercise. I feel these deaths should be investigated by physicians in an attempt to find a common thread in the deaths. A complete history, examination, and autopsy should be performed when such a death occurs. All observers should be questioned.

The only unequivocal finding is a history of an insect sting. Tests for IgE antibodies for insect venom on post-mortem blood can establish the fact that the dead person was in the 25 to 50% of persons who have the potential capacity to die from a sting. Of course, only a minute fraction with the potential for death will actually die from a sting.

Some patients upon autopsy will have laryngeal edema with obstruction, acute pulmonary edema, emphysema, and cerebral edema. These findings are non-specific.

Almost any system can be affected by insect sting reactions. I have had pathologists call me and give me their findings following a sting and ask me if this would occur after an insect sting. I replied in the affirmative. Sometimes the physician will not recognize the symptoms before death and the pathologist will not recognize the findings on the autopsy.

I would like to have any case of unexplained death sent to me, especially if it has been investigated and anaphylaxis is suspect.

Claude A. Frazier, M.D.
Doctors Park, Bldg. 4
Asheville 28801

To the Editor:

Many times it is difficult for a medical examiner or attending physician to determine if an individual has died from anaphylaxis due to insect stings, a food, or medication. In some cases the history is very clear and the event is witnessed; however, in many cases the evidence is not definitive. The usual differential diagnosis is anaphylaxis versus heart attack. Establishing the cause of death as anaphylaxis can be of significant benefit to the survivors, since most insurance companies consider anaphylaxis to be an accidental cause of death. In the case of insect sting allergy in particular and in reactions to many drugs and foods, anaphylaxis is mediated by antibodies of the IgE class, which are fixed to tissue mast cells. Some of the IgE antibodies are circulating in the serum, and it is easy to detect these antibodies by radioimmunoassay, even in post-mortem blood. We have recently demonstrated this for eight cases of anaphylactic death from insect stings.[1] In collaboration with the Office of the Chief Medical Examiner we have been attempting to demonstrate the appropriate IgE antibodies in blood specimens from suspected anaphylactic deaths since 1979. We have, however, missed a number of cases where either no sample was obtained or the case was not flagged to arouse the suspicion of the Medical Examiner's office.

Examples of known causes of anaphylactic death include stings from bees, yellow jackets, hornets, paper wasps and imported fire ants, some drugs, e.g., penicillin, chymopapain, asparaginase, and other protein drugs, and foods, particularly peanut, nuts, egg, fish, shellfish, milk, etc. Insect bites almost never cause systemic anaphylaxis, the only exception being reduviid bugs of the genus *Triatoma*. Remember that bites are not stings. Bites come from the front end of the organism while stings originate from the rear. Reactions to intravenous contrast media, local anesthetics, aspirin, sulfa drugs, foods like strawberries and wine, and food additives like metabisulfite and tartrazine are not mediated by IgE antibodies and cannot at present be detected by *in vitro* tests.

In cases of suspected anaphylactic death we will be happy to test blood or serum specimens to determine if the deceased was sensitive to the suspected allergen. There is no charge for this service. We cannot provide this service for living patients without a fee. The radioimmunoassay for specific IgE antibodies can only demonstrate that the patient fulfilled a necessary condition for anaphylactic death and does not prove unequivocally that anaphylaxis was the cause of death. The incidence of IgE antibodies against some allergens like stinging insect venoms runs as high as 50% in some segments of the population. IgE antibodies against foods and drugs are much less common and a positive finding can be much more significant in these cases. In our experience every witnessed anaphylactic death from insect stings has shown the presence of the appropriate IgE antibodies.

Specimens for analysis should be accompanied by a short history or copy of the medical examiner's report. They should be sent via first class mail to me.

Donald R. Hoffman, Ph.D.
P. O. Box 3294
Greenville, NC 27836-3294
Phone: 919/757-2816

Reference

1. Hoffman DR, Wood CL, Hudson P: Demonstration of IgE and IgG antibodies against venoms in the blood of victims of fatal sting anaphylaxis. J Allergy Clin Immunol 1983;71:193-196.

More on Words of Wisdom

To the Editor:

It was very kind of Dr. David Silber to refer in his letter in the July issue of the NCMJ (45:325-326, 1984) to my "Words of Wisdom" as a "jewel." He is entirely correct about the dynamics of their crystallization. My conclusions *were* the result of "vast experience over substantial time in an atmosphere of institutional heat and pressure."

There is a history and a cast of characters behind each of my admonitions. This is not the time or place to go into detail, but an essay could be written about each. I would not

dare publish many of the details in the NCMJ for at least a decade, some not in my lifetime, because I do not wish to defend myself against, even unwarranted, charges of libel. Dr. Silber may have suspected that admonitions 8-10 crystallized during a period when I was having an existential experience with our system of justice. If so, he was correct; and the period lasted for seven years. Never again!

I differ with Dr. Silber at only one point. He is very pessimistic where I am more optimistic about the value of education. I have lived long enough to observe that behavior *can* be modified if educational pressure is consistently applied over a sufficiently long period of time. It seems to me that this is the important historical truth that our species has documented since it invented language some millenia ago.

John B. Graham, M.D.
UNC School of Medicine
Chapel Hill 27514

Diabetes Day

To the Editor:

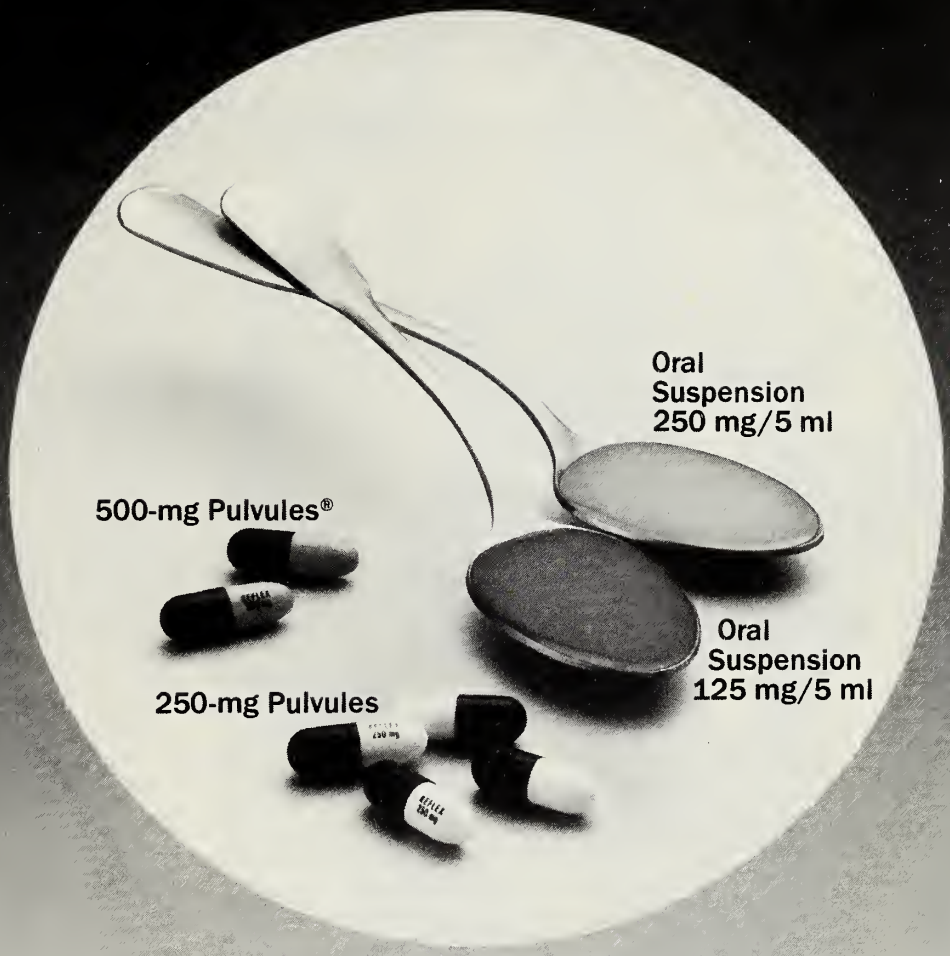
Insulin-dependent diabetes is a chronic illness which affects several thousand children and adolescents in North Carolina and neighboring states. In the last several years there have been revolutionary changes in the approach to treating this illness and there is great hope that the future is considerably brighter than in years past.

In order to provide information about the latest recommendations for management of insulin-dependent diabetes, the Division of Pediatric Endocrinology at Duke University and the North Carolina Affiliate of the American Diabetes Association are sponsoring Duke Diabetes Day on October 27, 1984. This program is designed for adolescents and children with diabetes, their families and friends, and the health care professionals who are involved in their care. Dr. Luther Travis will be the guest speaker and will address important issues in diabetic management and research. Information will be available about the new insulins and syringes. Pumps and instruments for home glucose monitoring will be displayed. Experts will answer questions about nutrition, control of blood sugar and importance of exercise. In addition, there will be activities for the whole family including games and prizes.

Duke Diabetes Day is designed to provide an opportunity to get to know one another. There is no charge. We would like physicians who care for children with insulin-dependent diabetes to notify their patients about Duke Diabetes Day and to join us on October 27. For more information, please contact Dr. Nancy Friedman, Duke University Medical Center, Box 3080, Durham 27710.

Nancy Friedman, M.D.
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Duke University

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MS can be mild. Or it can be severe. Once you've got it, you've got it for life. Most days, Nancy Ray can get around with a walker. With a lot of time and effort, she can even prepare meals for her family. Some people with MS aren't that fortunate.

The National Multiple Sclerosis Society is helping people with MS live with MS. And funding research for a cure all over the world. We can do it, but only with your help.

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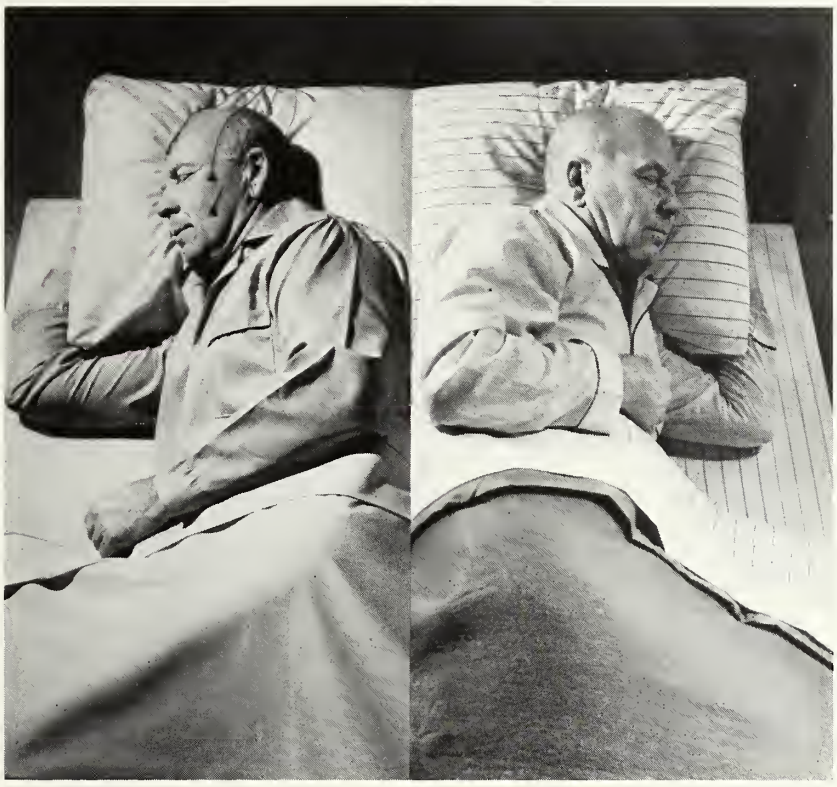
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Caution patients about driving, operating hazardous machinery or drinking alcohol during therapy. Limit dose to 15 mg in elderly or debilitated patients. Contraindicated during pregnancy.

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References: 1. Kales J *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971. **2.** Kales A *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A *et al: Clin Pharmacol Ther* 19:576-583, May 1976. **4.** Kales A *et al: Clin Pharmacol Ther 32*:781-788, Dec 1982. **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **6.** Kales A, Kales JD: *J Clin Pharmacol 3*:140-150, Apr 1983. **7.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **8.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **9.** Amrein R *et al: Drugs Exp Clin Res* 9(1):85-99, 1983. **10.** Monti JM: *Methods Find Exp Clin Pharmacol 3*:303-326, May 1981. **11.** Greenblatt DJ *et al: Sleep 5*(Suppl 1):S18-S27, 1982. **12.** Kales A *et al: Pharmacology 26*:121-137, 1983.

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Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

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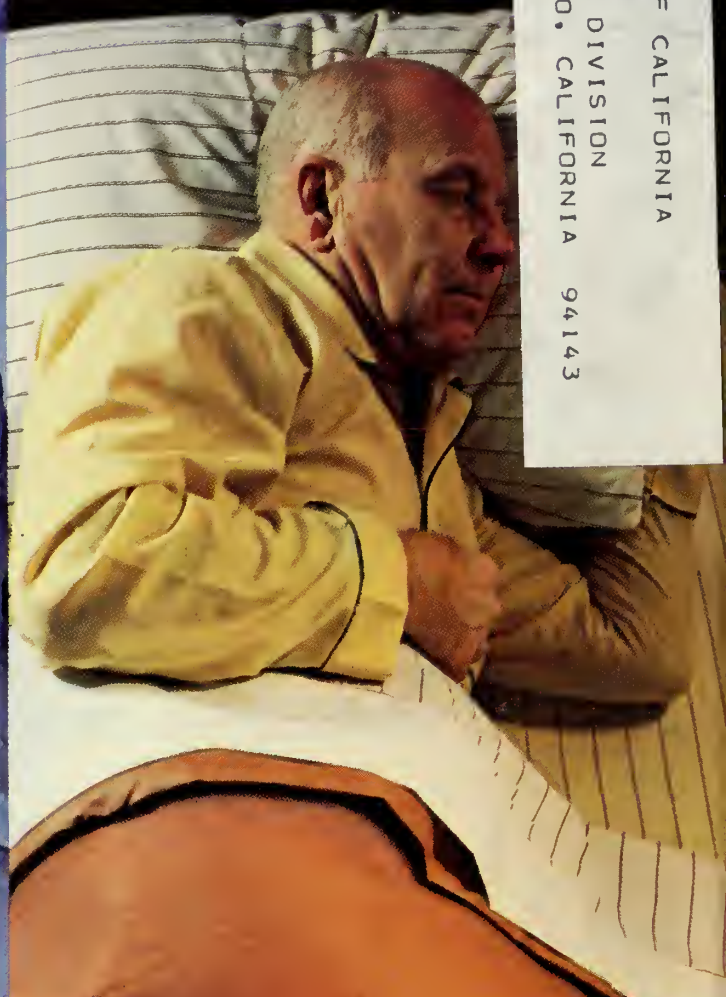
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The Official Journal of the NORTH CAROLINA MEDICAL SOCIETY October 1984, Volume 45, No. 10

New Hanover Memorial Hospital

Emile E. Werk, Jr., M.D. has gathered and edited ten articles in this issue of the *Journal* from New Hanover Memorial Hospital in Wilmington.



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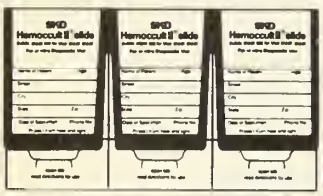
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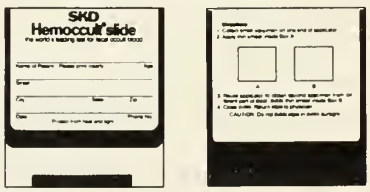
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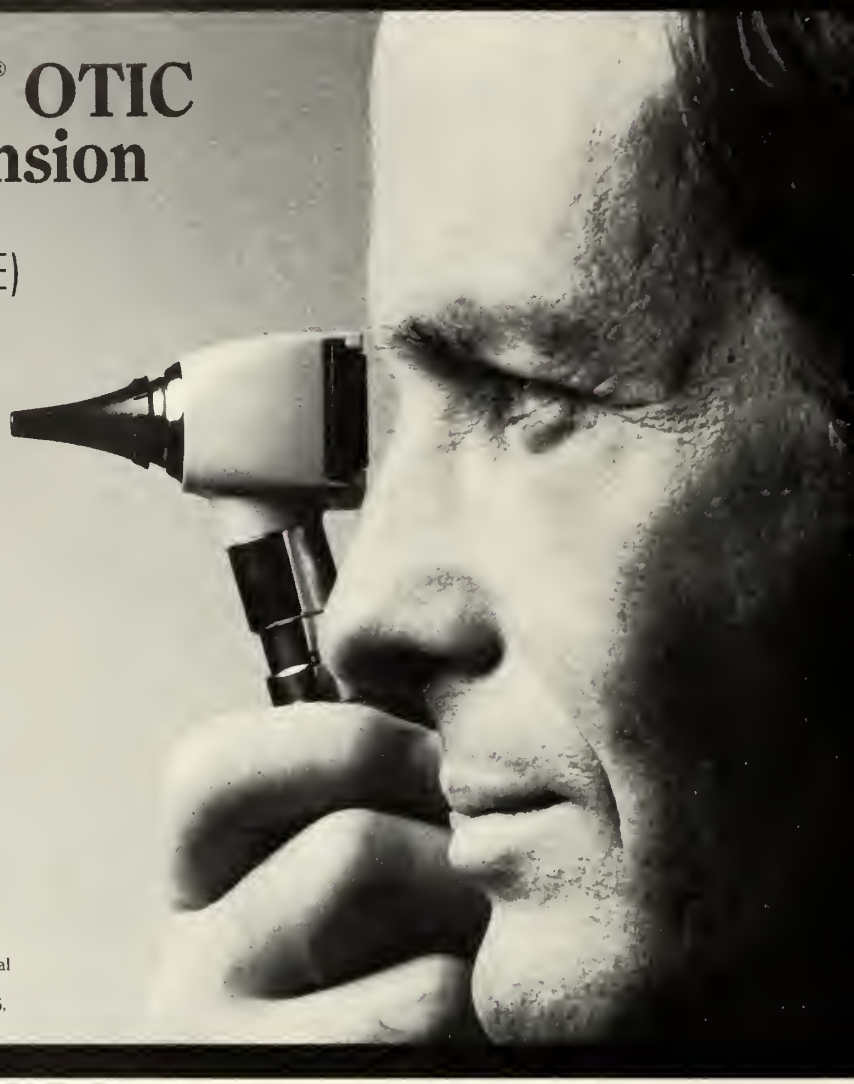
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Adapted from Cassisi et al.[1]

REFERENCE:

1. Cassisi N, Cohn A, Davidson T, et al: Diffuse otitis externa: Clinical and microbiologic findings in the course of a multicenter study on a new otic solution. *Ann Otol Rhinol Laryngol* 86(suppl 39, pt 3):1-16, 1977.



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SPECIAL ARTICLE

Walter Reece Berryhill: Physician, Medical Educator, and Innovator

William B. Blythe, M.D.

WALTER REECE BERRYHILL was born on October 14, 1900, in his father's home, then located on a site that later became a runway for Charlotte's Douglas Airport. He attended school at the old Dixie High School in Charlotte where he became thoroughly grounded in, among other things, Greek. He at first planned to go to Davidson College but later changed his mind in favor of the University of North Carolina after visiting Chapel Hill as a member of his high school's debating team.

Descended from a long line of Scotch-Irish Presbyterians, noted for their strong sense of duty and decided Calvinistic tendencies, it is not surprising that he started out to be a Presbyterian minister. For those of us who knew him, it is also not surprising that when he did not become a minister, he became a zealous proponent and staunch defender of his other religion — the University of North Carolina and its medical school. For Dr. Berryhill, there was no better job or higher calling than the deanship of the University of North Carolina School of Medicine.

Together with my father, he came to Chapel Hill as a freshman in the Fall of 1917, a member of the famous class of '21 which supplied the state and nation with leaders in many fields. Three of Dr. Berryhill's life-long characteristics became clear during his undergraduate days: his intelligence, his high quality as a leader, and his ability to stimulate in others a sense of loyalty to him, the result of his loyalty to his colleagues. He was elected to Phi Beta Kappa; won the Eben Alexander prize in Greek; was president of the Student Council and of the senior class; and was an Assistant Editor of the *Tar Heel,* the student newspaper.

The 1921 *Yackety Yack* says this about him, "We want to remember you not only as Berryhill, Phi Beta Kappa, President of '21 and the rest, but as Reece, who could pass a pleasant and jovial smile, whose laugh was free, whose heart was ours, and (one) of whose leadership we were proud."

Some time during his college years, Dr. Berryhill decided that he could be of more service to people as a physician than as a minister. He changed his courses accordingly, but had to teach public school for two years after graduating to repay an obligation to the state from which he had received financial support. The obligation was discharged by teaching in the Big Springs School of Mecklenburg County the first year and in a private academy in Charlotte run by Major Baird the second year. Here he established friendships with people who were later to be very helpful when he became dean of the medical school in Chapel Hill.

Dr. Berryhill returned to Chapel Hill in 1923, spent two years in the medical school and, as was the custom with the top students, transferred to the Harvard Medical School from which he was graduated in 1927. He spent two years as a house officer on the Harvard Medical Service of the Boston City Hospital, then entered private practice and spent about six months in Belmont, North Carolina with a Dr. Pressly. While practicing in Belmont, he was asked by Dr. Isaac Manning, then Dean and Professor of Physiology, to come to Chapel Hill to teach the course in physiology because of Doctor Manning's illness. Despite protestations of an inability to teach physiology, he returned to Chapel Hill for about six months in 1929-1930 as an Associate Professor of Physiology.

A cousin of Dr. Berryhill's and a fellow Mecklenburger, Dr. Joseph Wearn, became Chairman of the Department of Medicine at Western Reserve School of Medicine in 1929. At his invitation, Dr. Berryhill moved to Cleveland to become his first Chief Resident.

Several months after arriving in Cleveland, Dr. Berryhill made the most important trip of his life — to become married to Miss Norma Connell of Warrenton, North Carolina. They had met some ten years earlier while she was a student at Peace College, and their friendship flourished when they were students together in Chapel Hill from 1923 to 1925.

They were married in Warrenton on August 2, 1930, forming a partnership that was undoubtedly most important in the future development of the four-year medical school in Chapel Hill. Only those who know Mrs. Berryhill well know of her importance in the partnership. Her modesty, her sense of humor, and her devotion to Dr. Berryhill and the University all serve to belie the multifaceted critical role that was hers.

Return to Chapel Hill
The Student Health Service

Some time in 1933, Dr. Berryhill received a letter from Dr. Frank Graham, President of the University of North Carolina, requesting that he return to Chapel Hill to become head of the Student Infirmary, Dr. Abernathy having died suddenly. He accepted the offer and stayed in Chapel Hill for the rest of his life. The title of his first job was Director of Student Health Services and Physician-in-Chief, University Infirmary. One of his first acts was to recruit Dr.

From the Department of Medicine, University of North Carolina School of Medicine, Chapel Hill 27514.

Edward Hedgpeth as his Associate Director. Dr. Hedgpeth succeeded him as Director in 1941 and served the University for another quarter century. Dr. Berryhill was also an Assistant Professor of Medicine which meant in those days that he taught the second-year course in physical diagnosis.

In 1937, Dr. William deB. MacNider became Dean of the Medical School succeeding Dr. Charles Mangum. One of Dr. MacNider's conditions was that he be relieved of routine administration. To this end he recruited Dr. Berryhill as Assistant Dean in charge of student affairs with responsibility for admissions, guidance and counseling of students, and the transferring of students to the four-year schools. These duties were in addition to those of directing the clinical courses offered in the second year and running the Student Health Service.

Dr. MacNider never warmed to the deanship. His primary interests were research and teaching, and attending meetings elsewhere. The problems of University administration interfered with these interests, so he resigned as dean in 1940. Dean Robert House and President Frank Graham asked Dr. Berryhill to act as dean during the year 1940-1941, while a committee sought a replacement for Dr. MacNider.

Uppermost in the deliberations of the committee was the future of two-year medical schools. They concluded that such schools were insecure in the long run and that the University of North Carolina should begin planning for expansion to a four-year curriculum. Having reached this conclusion, the committee recommended Dr. Berryhill as the best person to accomplish this goal.



Figure 1. *The newly appointed Dean, 1940s.*

Becoming Dean

After initially declining the position, Dr. Berryhill agreed to assume the deanship for a period of five years, a length of time that he felt was reasonable for determining the real commitment of the university toward expanding the school. Dr. Berryhill later wrote that the decision was made only after he had received a firm commitment from the administration that a primary goal of the university was to expand the medical school when adequate financing became available, and that it would seek the funds required from the state and from private sources. The administration further agreed to provide immediately an increased budget to strengthen the basic science departments of the two-year school and to improve the teaching in the introductory clinical courses of the second year.

A quote from Dr. Berryhill illustrates his modesty and his loyalty to his teachers and to the University: "Even with these commitments on the part of the administration, it should be stated that the determining factor in the acting dean's decision to accept this responsibility — which he did not wish and which he was ill prepared to discharge — was the insistence of Dr. Isaac Manning, Sr. that this had to be his decision if the future of the school was to be made secure by its expansion to a four-year status."

The decision had hardly been made when the U.S. entered World War II and faced more immediate problems. Within three months after he became dean — shortly after January 1942 — the school announced the adoption of an accelerated program to enable students to complete the work of the first two years in eighteen months, i.e., vacations disappeared. This necessitated two changes which had to be effected almost overnight: (1) changing the schedule so that it correlated with those of the four-year schools, and (2) introducing new subject matter pertinent to military medicine. All of this was accomplished in less than six months so that by June 1942 the school began admitting students every nine months, a practice which continued until war's end. This remarkable feat, accomplished by all the U.S. medical schools, was done in the face of a faculty manpower shortage and the near impossibility of recruiting faculty members in wartime, especially to a two-year school. Dr. Berryhill wrote of this time with characteristic understatement, "all of this was done without too much hardship on either faculty or students. Both accepted the necessary adjustments, the longer hours and the added strain in a fine fashion and attempted to make the most of the situation." It should be pointed out that both students and faculty thoroughly enjoyed the long vacation between April and September 1946 when it finally arrived.

The Campaign for Expansion

Despite the trying and taxing times, Dr. Berryhill began to develop and execute the strategy that eventually led to a four-year school. Concurrently, he organized what he referred to as "discussions" among influential faculty members and university administrators, influential medical alumni, members of the Board of Trustees of the university, and leaders of the State Medical Society. He worked

away steadily on this project during the war years.

The result of these "discussions" was a committee appointed by President Frank Graham and headed by Dr. Paul McCain, the head of the Tuberculosis Sanitorium System. The committee's charge was to develop a proposal which could be discussed with Governor Broughton and, if he concurred in the proposal, could be presented to the Board of Trustees of the university for their consideration. (In those days the Governor was chairman of the Board of Trustees.) The essence of the McCain committee's proposal was that there should be state support for expansion of the medical school to four years and for the construction of hospitals in rural areas and in areas where hospital facilities were inadequate in size or already too outmoded to meet the demands for adequate medical care.

Governor Broughton enthusiastically endorsed the proposal of the McCain committee and presented it to the Board of Trustees of the Consolidated University. The trustees unanimously approved the proposal — now Governor Broughton's proposal — and authorized the appointment of a state commission "to study all aspects involved" and charged it with submitting recommendations for implementing the outlined goals to the General Assembly in 1945. Governor Broughton appointed Mr. Clarence Poe, publisher of the *Progressive Farmer,* Chairman of the commission which became known as the Hospital and Medical Care Commission (HMCC).

The HMCC spent almost eight months in study. Early in October 1944 it adopted a report for submission to Governor Broughton and appealed to the people of the state for their support in its implementation. In brief, the report delineated in well-documented fashion the need for more doctors, more hospitals, and more voluntary insurance plans to cover hospital and medical care costs.

In November 1944 Governor Broughton arranged to have the recommendations of the HMCC presented to the Advisory Budget Commission in preparation for action by the 1945 General Assembly. The Advisory Budget Commission took the position that since this was an entirely new undertaking of great importance to the people of North Carolina and one which would result in the commitment of a large amount of money, the General Assembly should decide about whether to implement the recommendations.

The General Assembly of 1945 formally established the North Carolina Medical Care Commission (NCMCC) and appropriated funds for loans to students in the medical schools of the state who would agree to practice in rural areas, and authorized the trustees of the university to expand the medical school to four years. However, an amendment was appended to the legislation which requested further study by a group of experts from outside the state to determine the best location for the four-year school before the authorization could be implemented. This resulted in the appointment by the Medical Care Commission of a National Committee headed by Dr. W. T. Sanger, president of the Medical College of Virginia, to study the question of the best location for the proposed four-year school and hospital. Furthermore, the legislature's charge was expanded by members of the NCMCC who opposed expansion of the school to include a study of the *need* for an expanded school.

The majority of the Sanger Committee recommended that the School of Medicine of the University be expanded and that it be located in Chapel Hill. Furthermore, the committee recommended that the functions of the medical school be broadened, and emphasized the importance of regionalization in the delivery of medical care in the state.

Dr. Berryhill wrote of this time 1945-1947, "While the majority of the commission approved the recommendation and worked steadfastly for the next two years to bring about favorable action by the 1945 and 1947 General Assemblies, there was far from unanimity of agreement among its members on the two major issues — the use of state funds for hospital construction in communities deficient in hospital beds and the expansion of the university school of medicine with the construction of a university hospital at Chapel Hill."

The lines were quickly drawn, and a battle began which raged throughout the state with considerable fervor — even ferocity. Its effects were evident for some years following the action of the 1945 and 1947 General Assemblies, which finally passed legislation which implemented essentially all of the recommendations of the Sanger Committee. (The battle over establishment of the State's second medical school at East Carolina was pale by comparison.)

Initially, some members of the medical profession, as well as civic leaders, felt that state funds to assist in the construction of community hospitals meant state control and therefore constituted socialized medicine! Another and rather powerful group was concerned about the cost of constructing community hospitals and especially the cost of building and operating a four-year medical school and teaching hospital within the university. Enthusiasm was also lacking among many elements of the Arts and Sciences faculty at Chapel Hill. The location of an expanded school once again became the focus of debate, as it had frequently been over the past fifty years.

Some felt that North Carolina did not need three medical schools, and that the two privately endowed schools, Duke and Wake Forest, could supply the needed doctors and health personnel without a large expenditure of tax funds. Representatives of these schools — faculty, alumni, and others — urged the appropriation of state funds for physical enlargement and increased operating budgets at the private institutions rather than state appropriations for the expansion of the University of North Carolina two-year school.

Finally, in March 1947, the legislative Joint Appropriation Committee, after hearing long and impassioned arguments from both sides, approved the permanent improvements appropriation for the university, which included the funds requested for expansion of the medical school and construction of a hospital to be located in Chapel Hill. At Governor Cherry's suggestion, however, only planning funds were to be appropriated until the post-war inflation had subsided ("when we can get a dollar's worth of construction for a dollar"). Observing the continuing inflation, the subsequent Legislature released the funds.

Meanwhile, another obstacle appeared. A group from Greensboro offered the potential Moses Cone Hospital as the primary university hospital together with a substantial endowment. The idea was that the medical school move to Greensboro and become intellectually based on the

Woman's College of the University. After much discussion, this offer was declined by the university, and plans for the development at Chapel Hill moved swiftly onward.

Expansion of the Medical School

The period of 1948-1954, marked at the beginning by development of plans for the four-year school and at the end by graduation of the first four-year class, was both exciting and trying for Dr. Berryhill. The two most important undertakings of this time were the actual physical expansion of the Medical School, including the building of the North Carolina Memorial Hospital and recruitment of faculty and staff necessary for operating the clinical departments and the hospital.

Despite unforeseen difficulties, including optimistic underestimates of cost and continuing inflation, which initially resulted in insufficient funds for physical expansion, the necessary money ($5,000,000) was finally obtained and construction began in November 1949, the hospital opening in September 1952.

Dr. Berryhill's ideas about the type of faculty needed for the four-year school were undoubtedly a major factor in the success that the medical school has achieved. This is what he wrote later about the criteria used in selecting chairmen for the clinical departments: "In selecting the chairmen of the clinical departments in 1951-1952, certain criteria were insisted upon — criteria which by 1969 might have been, in all too many instances, considered outdated in many schools of medicine, including perhaps this one. Those criteria were: (1) excellence as a clinician and active participation in the care of patients; (2) superior teaching ability and devotion to this responsibility with respect to both undergraduate medical students and to interns, residents, and fellows; (3) competence in clinical research; (4) evidence of a desire and motivation to work with others for the improvement of medical education at all levels in the medical school; and (5) possession of a sense of responsibility to the university and the state of North Carolina."



Figure 2. *Addressing the first graduating class of the four-year medical school, 1954.*

In spite of many difficulties, all four medical school classes were in residence at Chapel Hill in 1954, for the first time in the history of medical education at Chapel Hill, and for the first time since 1910, the university awarded the Doctor of Medicine degree. Graduation day marked the achievement of what Dr. Berryhill considered his major life goal.

He continued as dean of the medical school for another decade, a time that saw the school develop into one of major national prominence, although not without turbulence. John Graham, who participated in many of these events, describes them elsewhere.

The Third Career

Dr. Berryhill resigned the deanship in 1964, and after a year's leave of absence during which time he was a Commonwealth Fund Traveling Fellow, he began a third successful career which was also dedicated to the health of the people of North Carolina. He became the first director of a newly-formed division of the medical school, The Division of Education and Research in Community Medical Care. As its title suggests, this division's major objective was to improve the mutually beneficial relationships between the medical school and the local communities in the state. Specifically, Dr. Berryhill considered that the division should be concerned with improving the methods of continuing education for physicians in their own hospitals; and in developing joint university-community hospital teaching services in various types of clinics and hospitals. The objective was to provide a better balance in the educational experience of undergraduate medical students, interns, and residents, as well as the medical faculty, by providing an opportunity for all to become more knowledgeable about problems of medical care in the community. He was also interested in initiating studies and consulting about methods by which medical care could be more effectively delivered to the communities in the future.

The work of this division set the stage for the Area Health Education Centers program in the state, a program that is now recognized as one of the most effective and outstanding of these programs in the nation. David Citron describes the AHEC activities in his contribution.

Dr. Berryhill officially retired from the University in 1973, but remained active in the affairs of the medical school until his death on January 1, 1979. In fact, until

shortly before he died, he was intimately involved in the planning for the centennial celebration of the School in February, 1979.

I shall conclude this account by quoting what I wrote about Dr. Berryhill after his death in 1979: "These are some of his accomplishments, but the man was much more than these. For those who knew him, he was the embodiment of dedication, integrity, loyalty, and selflessness — qualities which assumed saintly qualities when one was in accord with him, and which might have been thought of as inordinate Scotch-Irish contrariness in disputatious matters.

"But whether or not all might not have agreed with him all the time on specific issues, all ardently agree that Doctor Berryhill was totally dedicated to his beloved university and medical school — as well as to his state — and that they are all nobler because of him.

"As is the case with many great men, he did not stand alone. Throughout his professional life, he had the help of an equally dedicated, perceptive, modest person — Mrs. Berryhill. Together — and synergistically — they made the four-year medical school at Chapel Hill."

A Personal Note

The first time that I recollect hearing of Dr. Berryhill was in early 1944 when I was 15 years old and a senior in high school. I remember the occasion vividly. My father and I were having a discussion in an upstairs bedroom about what I might like to do with my life. There was much talk about going to the U.S. Naval Academy or of becoming some sort of forest ranger, two romanticisms that were appealing to me then.

Somehow, neither of these notions — as well as some others — were entirely satisfying either to me or to my father! I finally decided that a career in medicine might be the answer. It seemed to offer the possibility of combining my interest in natural science with an ill-formed, but nevertheless compelling, adolescent altruism.

The discussion ended promptly. My father said, "You have made a fine choice. Now, we need to write Reece Berryhill — he's now Dean of the Medical School at Chapel Hill — and find out what you should do to prepare yourself." My father wrote to Dr. Berryhill and sometime later a letter arrived from him. As I reflect on it, the essence of the letter was the essence of Dr. Berryhill. First, he expressed delight in hearing from my father, a friend since their Chapel Hill days; next, he expressed delight in hearing that my father had a son who was interested in studying medicine; he then prescribed in general terms what I should do to get ready for medical school; and he ended up by describing briefly, and in somber terms, the nature of the problems of the Medical School and the University and what had to be done to overcome them.

Thus, he had expressed genuine friendship and loyalty to an old friend, offered candid, straightforward advice to a student, and outlined the problems — not the accomplishments — of the Medical School and University to a citizen of the state.

There is no telling how many letters like this that he wrote.

It was not until his last years that I was able to spend much time talking to Dr. Berryhill. Then I would go to his office frequently and seek his advice and opinion on many things. He never changed. He continued to be interested in medical students and prospective medical students; his love for the Medical School and University were never dimmed and distorted by an old man's bitterness (although he still had sharp words for some happenings that he did not like); he never spoke of his accomplishments; and he continued to give me candid, straightforward advice. He was a remarkable man!

SPECIAL ARTICLE

Walter Reece Berryhill: Dean of Medicine, 1941-1964

John B. Graham, M.D.

As Bill Blythe has pointed out, Dr. Berryhill was Dean of the Medical School at Chapel Hill for 23 eventful years and should be regarded as the architect of the four year school of medicine.[1] His charge had been to bring about the metamorphosis of a small, regional, two-year school of medicine into a comprehensive medical center. This was to be accomplished in a venerable state university with strong traditions, and with vested interests in the arts, humanities, and social sciences which would be greatly threatened by the change. There would probably be turmoil and strife, and it would be necessary both to maintain strong political support within the state and to recruit an outstanding faculty from the national pool. Accomplishing such goals would require a remarkable person. Walter Reece Berryhill proved to be the right person at the right time in the university's history. He accomplished his

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[1] I never addressed him other than as "Dr. Berryhill," and to me and many of my contemporaries he will always be THE DEAN.

monumental task, but it was not without travail as I shall recount.

I was a member of the faculty for 18 of the 23 years of Dr. Berryhill's deanship and worked on many of his projects. I never knew exactly how he viewed me, because we were very different in attitudes and temperament, but we shared a devotion to the institution. He seemed to turn to me when there was a particularly sticky problem which others shied away from. He must have known something about me which I didn't know about myself.

A Man of Character and Determination

Dr. Berryhill was large and imposing. He had a simple sense of humor and lacked a light side. Every conversation I ever had with him sooner or later became serious, usually coming around to our mutual concern with the less than satisfactory state of university affairs. Both of us had been reared as Presbyterians and had similar views about Original Sin as it affects all human, and especially university, activities. Our wives must have become very weary of hearing us discuss the venality and incompetence of our masters. The university was Dr. Berryhill's "religion," if by religion one means what Paul Tillich meant, "that which means more than anything else." He must have seen in me someone equally committed, because he repeatedly challenged me to take actions in the larger university arena which he could not take because of his position. (See "Revolt of 1956"; "Holman Committee") I usually rose to the bait, because, I suppose, it played to my suspicion that I was faint-hearted. He was very clever!

Dr. Berryhill possessed *gravitas* in full measure, a quality which automatically induces respect in others. One knew instinctively that he was completely serious and that levity had no place in a business discussion. This gave him a power with subordinates that I have seen duplicated in few others.[2] I once heard him say that he could judge a person's motives and quality by listening carefully to a conversation. At the time, I suspected that he used this as an excuse to hide the exercise of his prejudices, because there seemed to me to be insufficient data in conversation to reach a judgment. Now I realize that he was extraordinarily astute and usually reached correct judgments about people, although not entirely from conversation. He must have developed his interview technique empirically, because I never heard him quote an authority for the view that conversation provides a window on the mind. If his *gravitas* and impassivity had the same effect on others that they had on me, he must have obtained a great deal of information which interviewees had not initially intended to transmit.

A key feature of Reece Berryhill's leadership was his attitude toward "administration." He believed that it should be kept to a minimum and prevented from interfering with more important matters. The fewer people involved the better. He operated the School with a minimum of assistance: Mrs. Privette, then Miss Dunlap, and finally Miss Dunlap and her several assistants, never numbering more than a half-dozen. He made decisions with ease and without fuss. Philip Manire, a long-time medical faculty member and now Dean of the Graduate School, says that Dr. Berryhill not only disdained administration, he lost respect for anyone who aspired to an administrative career. He did not deign to train assistant deans, believing that administration consisted of the application of common sense and that any good person could do it. He tried to avoid long business and committee meetings and developed an effective technique. If one asked for an appointment, he often replied that he preferred to drop by one's office. This allowed him to break off a discussion whenever he wished by suddenly remembering another appointment.

Dr. Berryhill was a man of his word. If he made a commitment, he kept it. This meant that he had to consider a proposition carefully before agreeing to it. Although this required great mental energy, he did not procrastinate. He was a prodigious worker. As a leader, he knew that he could only point the way to others. It was their responsibility to do their own jobs as carefully as he did his. This style of leadership meant that he must know well and possess the confidence of those he was trying to lead. He accomplished this by using a variety of social mechanisms to meet and get to know his faculty. The Berryhills gave many parties and, with Southern gentility, always called when tragedy struck. I doubt that anyone who joined the faculty while he was Dean failed to receive at least one invitation to dinner. I recall how downcast he was when he realized that the faculty had become too large to be entertained all at once!

Mrs. Berryhill was equally concerned about the welfare of the families of new faculty members. She saw to it that their wives became informed about the affairs of the community, and became involved, if they wished, in the many worthwhile service committees. Such committee work is no longer as fashionable as it once was, but the present generation has apparently re-invented the wheel under the rubric "support groups," which accomplish the same ends. The Berryhills were a formidable pair and earned the devotion of the large group of newcomers to the school who arrived during the 1950s. This devotion stood Dr. Berryhill in good stead in the mid-1950s when there was an abortive attempt to unseat him, a misguided affair which led to the faculty "Revolt of 1956" about which more will be said later.

It has been my observation that the possession of strong emotions is characteristic of those who accomplish great things, and Dr. Berryhill is one of my examples. He kept his emotions in strong check, but they erupted occasionally. When this occurred, he was apt to make errors in judgment. He was strong enough, however, to reverse a bad decision without loss of face when he had cooled down. Mrs. Berryhill says that he could do this because "he knew who he was." I agreed. He was, in David Reisman's phrase, "inner directed." When he thought he was right, he didn't care what anyone else thought.

Preparation for the Deanship

I had not been conscious as a premedical student at Davidson that there *was* a medical school at UNC. Duke Medical School, then 8 years old, was new and attractive and I applied and was accepted. But my roots were deeply embedded at Chapel Hill, and my family and friends urged

[2] Dr. Charles Burnett, our first Professor of Medicine, also had this quality. Dr. Burnett's subordinates often referred to him — beyond his hearing — as "Steely Blue Eyes."

and finally convinced me to switch schools. I was assured, correctly, that transfer would be a simple matter, and went to Chapel Hill in July 1938 to investigate. I was directed to the Student Health Service, then in Abernethy Hall, where I met a tall, serious, white-coated doctor, the medical school's Assistant Dean, who asked several direct questions.

"Why do you want to transfer from Duke?" "I think I would be happier here."

"Are you a good student?" "I have a better than B average in my sciences, and made straight A's my senior year."

"Do you have your transcript with you?" "No, but I can get one."

"Don't bother, I'll do it. You'll hear from me in a few days."

The interview lasted less than ten minutes, and a week later I received a telegram from Dr. Berryhill informing me that I had been admitted. I suppose a committee might have met, but it is more likely that he had made the decision himself. It would have been in character for him to have spared others the trouble of involvement in such a trivial matter.

As a student, I had few contacts with Dr. Berryhill, who was both Director of the Student Health Service and Assistant Dean of the Medical School. My recollection is that he spent mornings at the Infirmary holding sick call, and afternoons running the Medical School.[3] I thought that I was, perhaps, unique in seeing so little of him. I learned years later that my classmates had had similar relationships with him. As a student I regarded him as austere and aloof. Now I view him as having been extremely busy, but concerned about his students and responsive to their needs. He simply lacked small talk and was not effusive. Three contacts with him during my student days 45 years ago are still bright in my memory.

Within a few weeks of matriculation in 1938 my class of 35 — medical students were not married in those days — were entertained by the Berryhills at their home on West Franklin Street. It was a bright Sunday afternoon in October. Their large home was on a slight elevation above what is now Fowler's Foodstore, and the beautifully landscaped lot sloped down to a creek over which a service station and Fowler's have been built since World War II. The grounds were spacious, the hosts were gracious, and the food was delicious. It was a delightful occasion.

Dr. Berryhill's course in Physical Diagnosis was unusual in one particular. He was a large man and had very thick fingers. When he percussed the boundaries of the heart for a group of students, the sounds changed so dramatically that one could almost see the boundaries. How I envied this talent of his!

My third memory is of an event on my last day as a student in Chapel Hill. It illustrates Dr. Berryhill's drive for continued improvement and his willingness to seek advice in unusual places. I had completed my examinations and was packing to go home. Suddenly I was informed that Dr. Berryhill wished to see me immediately. My heart almost stopped. What had I done? I ran up the hill from Whitehead Dormitory to MacNider and entered his office. He was seated behind his desk in front of the window, the inevitable cigarette in his hand. I examined him quickly for signs of anger, but he seemed to be his usual taciturn self. He proceeded systematicaly to extract my views of the adequacy of the medical school curriculum, and my opinion of the various courses and instructors. I was very reluctant in my youth to express my opinions, but since he had asked for them, he got them. Later I was very pleased to learn that he had taken many of my suggestions seriously and had acted upon them.

This habit of seeking advice from a wide range of advisors must have been a regular practice. When I returned from World War II — still in uniform and not yet on the university's payroll — the now Dean asked me to review and express my opinions about the curricula vitae of three men who had been short-listed for the Chair of Pathology, one of whom would become my Boss. I was baffled about how to judge them, but one thing is clear. Even then he was selecting chairmen with great eare. Two of the three men were Ken Brinkhous and Tom Kinney, both of whom became national and international figures in Pathology. He used the same standards later in selecting the clinical chairmen.

Dr. Berryhill hoped that every student who transferred elsewhere would do so without "culture shock." This was difficult because each of the about thirty schools to which we transferred had had a generally similar but slightly different set of courses in the second year. The variations were dutifully reported to him by the transferees and, because of his concern, he tried to introduce them into Carolina's curriculum. I suppose there were advantages for subsequent transferees, but the second year of the old two-year curriculum became saturated with courses in Public Health, Obstetrics, Pediatrics, Dog Surgery, etc. When the clinical faculty arrived in the early 1950s, it found a curriculum already geared to excessive clinical teaching in the second year, a condition from which it has never recovered.

After leaving Chapel Hill for Cornell in 1940, I remained in touch with Dr. Berryhill and he helped me to get my residency. He offered me a job in 1944 as I was finishing at New York Hospital, because the pathologist at Watts Hospital had been drafted and the Pathology department was having to assume the management of Watts' laboratories. Drs. Bullitt and Holman badly needed help, but I felt that I had to serve in the Armed Forces. I was able to help them recruit John Miale, but I think all of us knew that I would be returning to Chapel Hill after the War, if I survived and there was a place for me.

The Deanship: Early Years

Except for a visit to Chapel Hill while I was recuperating from hepatitis in 1944, I did not see Dr. Berryhill between 1940 and 1946. During the war years he was largely occupied by the accelerated educational program and laying the groundwork for the campaign for the four-year school. My colleagues, Dr. Citron and Miss Dunlap, were present

[3] I have since learned that Dr. MacNider agreed to be designated Dean only if his duties were limited to participating in policy decisions and attending ceremonies.

then, and we must depend on them for information about those days.

I joined the university faculty as an instructor in the fall of 1946 at a time when appointment to an assistant professorship was automatic if one possessed a terminal degree, unless the degree happened to be an M.D. and its possessor a member of the medical faculty. Dr. Berryhill had been reared in the austere Harvard and Western Reserve traditions wherein one remained an instructor, often unmarried, until ready to become a department head or dean. When he hired Ted Blount, Lytt Gardner, John Riggsbee and me as instructors in 1946-47 at $300/month, I was still in uniform and on terminal leave. I was happy to have a job to help support my wife and child. The others were planning to practice medicine, but I was planning to teach. I was, therefore, assigned extra duty. In addition to teaching three quarters each year, I was also placed for 3 years on the overworked Admissions Committee which had the job of selecting 50 medical students each year from the huge pile of applications being submitted by returning veterans.

The fall of 1946 was very exciting. The Legislature, scheduled to convene in January 1947, was to receive and consider the recommendations of the Sanger Committee. This out-of-state body had recommended that the state convert the two-year medical school at Chapel Hill into a four-year school, establish a related university hospital, and start new schools of Dentistry and Nursing. Together with the existing schools of Pharmacy and Public Health, this would provide the state with a panoply of health science institutions. It was the four-year medical school over which blood was destined to be spilled, but the Sanger Committee also recommended the establishment of a statewide network of related hospitals based upon a central unit in Chapel Hill. Having just spent six years in New York and the Army, I cynically assumed that the concept of a statewide hospital network was merely campaign oratory whose purpose was to assure the acquisition of the four-year school. Time has proved me wrong. It was this recommendation which lies behind the establishment of the AHECs, which Dr. Berryhill was to bring into existence in the "fulness of time." He actually had three separate careers at Chapel Hill: Director of the Student Health Service, Dean of the Medical School, and originator of the AHECs. The one for which he is best known is the medical deanship, the task on which I served with him. But when he retired, he tackled the unfulfilled part of the Sanger report and established the hospital network. This development is described elsewhere by Dave Citron.

Bill Blythe has described the political campaign for converting the medical school into a four-year curriculum, a movement that had been underway for many years. Dr. Berryhill had worked very hard on the project, and it was successful. The Sanger report was approved by the 1947 legislature, and planning funds were appropriated. Building funds were provided in 1949, and the North Carolina Memorial Hospital — a memorial to the dead of both World Wars — opened in 1952.

While the hospital was being built, Dr. Berryhill spent most of his time recruiting the clinical faculty. His method was simple: recruit first class department chairmen and let



Figure 3. *The department heads, 1954.* Front row: *D. A. Macpherson (Bacteriology), James Andrews (Biochemistry), Nathan Womack (Surgery), Robert Ross (Obstetrics), William Richardson (Continuing Education), Kenneth Brinkhous (Pathology), George Ham (Psychiatry).* Back row: *Thomas Butler (Pharmacology), Charles Hooker (Anatomy) William Fleming (Preventive Medicine), Edward Curnen (Pediatrics), Reece Berryhill (Dean), W. C. George (Anatomy), Charles Burnett (Medicine), Robert Cadmus (Hospital Administration).*

them do the rest. He scoured the entire country for chairmen, taking full advantage of his contacts in the foundations, and in Boston and Cleveland. He was spectacularly successful. Duke's Dean Wilburt Davison, perhaps in a burst of hyperbole, is reported to have said that Berryhill had brought together the best group of clinical department heads since Welch had established the Hopkins with Osler, Halsted, McCallum, etc. Dean Davison may have exaggerated, but the achievement was real and has been lasting. Dr. Berryhill succeeded in a single stroke in changing a small but good, regional teaching institution into one that aspired to be a comprehensive medical center with national standards in teaching, research and patient care. But it was not all smooth sailing as we shall see. Dr. Berryhill made a negative decision in 1949 whose effects hampered him for the rest of his deanship.[4]

The Deanship: Later Years

The higher administration believed that an "Administrator" was required for the Division of Health Affairs, someone to oversee the health schools and the university hospital. The position was offered first to Dr. Berryhill. After consideration, he declined, arguing that organizing the medical school properly was as much as he could handle, besides he knew nothing about the methods and standards of the other disciplines.

In retrospect, this was probably a mistake. His two major contributions — the successful political campaign and the recruitment of the clinical chairmen — had been largely completed by 1950, and as time has shown, the job of Administrator of Health Affairs is largely ceremonial. He could probably have melded this position with the deanship and managed both, thereby avoiding the troubles to which his declination was to lead. I do not know that anyone considered linking the two positions, but since he was not interested, the administratorship of Health Affairs was offered to and accepted by a former student fifteen years his junior.[5]

The Administrator's experience had been in administering university hospitals rather than in practicing medicine and teaching medical students. He was very knowledgeable about and interested in medical care, but less so about the ordinary problems of medical education and medical research. On the other side, the clinical faculty was a vigorous, ambitious group of young doctors who were very interested in advancing their careers through teaching and research. The new organizational structures forced them into frustrating and wasteful inefficiencies. They had to deal with Dr. Berryhill on some matters and the administrator of the hospital on others, and the boundaries of responsibility between the two were very hazy. The conflicting goals and the strong personalities involved led to what I shall call the faculty "Revolt of 1956."

There were three issues: 1) Dr. Berryhill's suitability as Dean, 2) administrative control of the hospital, and 3) the status of the medical school within the Division of Health Affairs. By votes at a mass meeting, the medical faculty indicated its confidence in the Dean, requested that the university hospital be placed administratively within the School of Medicine, and indicated its unhappiness with the overall administrative structure. The resolutions led to a conference between a committee of faculty members and Chancellor House, Acting President Friday, Vice-President Carmichael, and Acting Dean of Law Aycock, who was destined to succeed Chancellor House. The faculty's request concerning the hospital was accepted, and Dr. Berryhill assumed responsibility for its operation. The issue of whether the School of Medicine was co-equal to the other schools of the Division or, because of its size and complexity, was entitled to special treatment, was not resolved until the Holman Committee's study of 1962-63[6] and the appearance of Chancellor Sharp, Aycock's successor.

Not all of the turbulence in the medical school in the mid 1950s was related to poor external relations. There was also a strong difference of opinion *within* the medical faculty about its own decision-making processes. This led to an episode in 1957 known at the time as "The Revolt of the Associate Professors," and Dean Berryhill supported the rebels!

It has been customary in European universities for each department to have a single PROFESSOR as head, or Geheimrat. This system was transplanted from Germany to Johns Hopkins and Chicago in the 19th century and became normative in American medical schools after the Flexner Report of 1912. The basic medical science departments at Chapel Hill were small before World War II, usually consisting of one older and one or two younger teachers. The elder was always a Professor and the younger teachers usually left for other jobs before reaching professorial age. Thus in 1950, it was natural to have only a single professor in each department of the medical school, although professorships were not limited in other departments of the university. The enlargement of the medical curriculum to four years and the need to teach dental and para-medical students led to much larger departments, some of which contained numerous Associate Professors. Dr. Berryhill had utilized the existing department heads, all professors, as advisors in enlarging the school. They had met regularly and had come to regard themselves as having an executive function. Several of them decided to try to impose the European professorial model on the medical faculty by the fiat of this quasi-Executive Committee. The Associate Professors, of whom I was one, were enraged and began agitating. We had been Dr. Berryhill's main support when he had been under fire the preceding year, while some of the department chairmen had not exerted themselves on his behalf. Dr. Berryhill opposed the coup, and the attempt

[4] His other advisors and I must share the blame. He and I discussed his pending decision on a bus between Colorado Springs and Denver while returning from the 1949 AAMC meeting. I was not experienced enough at age 31 to advise him wisely.

[5] Christopher Fordham held both positions successfully 3 decades later when the demands of administration were much greater.

[6] The Holman Committee was appointed by Chancellor Aycock in 1962 as the result of a motion which I made at a Faculty Council meeting. My motion was the substitute for another motion proposed by persons in the Division of Academic Affairs who were attempting to disenfranchise the faculty of Health Affairs, then constituting only about 10% of the faculty but clearly destined to become a near majority eventually. I was influenced into taking this action by Dr. Berryhill, and later served on Dean Holman's committee.

failed. Following this, he proposed a constitutional assembly.

Dr. Berryhill had attended the annual meetings of the Association of American Medical Colleges regularly and had concluded that university administrators were obtaining too much power over faculty members. He felt that faculty members should be shielded as much as possible from arbitrary acts of administrators, and proposed that the faculty develop a constitution and a set of by-laws. The committee he appointed to bring in a proposal was chaired by William Fleming. Walter Hollander was its secretary and Charles Burnett, Nelson Ordway and I, and several others did the donkey work. An instrument was drawn up which, when adopted by the faculty, gave it the right to establish (and dis-establish) departments and to adopt and alter curricula. It also defined the committee of department chairmen as "advisory to the Dean." This instrument has been the faculty's bulwark against arbitrary actions by a Dean or a cabal of department chairmen.

I have often wondered why Dr. Berryhill openly promoted the adoption of this mechanism of governance, one which down-played the importance of the department chairmen he had collected so carefully. Several possibilities suggest themselves. Some of the then current group of chairmen had either opposed him or had remained neutral when the issue was his continuation as Dean. He owed them nothing. Another possibility is that he was expressing his Calvinistic view that power tends to corrupt and must be restrained. The least charitable is that he did not want to be at the mercy of any group with the power to remove him. In any event, he succeeded in establishing a framework of governance for the medical school which leaves pedagogical matters entirely in the hands of the faculty, if they are willing to accept the responsibility.

What might be called Dr. Berryhill's "populist" attitude toward the faculty was shown in other ways. He used regular faculty meetings as a consultative forum and educational mechanism. Agenda were short. Only important issues were discussed. He encouraged free discussion, because he wanted to see how his ideas fitted with those of the faculty. There was always a final agendum, "Remarks by the Dean." Here he expressed his own views and feelings, particularly about political currents in the State and the university. His tone was usually somber, but his analysis often showed that there were potential openings here and there, although perhaps at low probabilities. One left a faculty meeting at 5 o'clock or 5:15 to deal with personal matters feeling that the Dean had his hand on the tiller and would alert us if the need arose.

The rapid growth of NIH occurred during Dr. Berryhill's deanship. The faculty competed well for research funds and our facilities quickly became strained. My memory of the late 1950s and early 1960s is of high scientific productivity under conditions of great crowding.[7]

The only buildings constructed during Dr. Berryhill's deanship after completion of the hospitals[8] were the Research Wing added to MacNider in 1962, and the Biological Sciences Research Center in 1964-65. Temporary relief was obtained during the middle 1960s during Isaac Taylor's deanship when the faculty were authorized to use house trailers for offices and laboratories.[9] The university administration kept a tight lid on additional space for the medical school, and permanent relief was achieved only in the 1970s after the medical student class size had been forced upward by Federal pressure to produce more doctors and local pressure to accommodate the maturing post-war "Baby Boomers."

By 1962, Dr. Berryhill had acquired an Assistant Dean of Students, because he had become too busy to handle student advising alone. When he decided to retire in 1963, statutorily a year early, he asked whether I would be willing to take over the duties of his assistant dean. I looked the situation over and decided that what was needed was a set

[7] Professor Parkinson, author of "Parkinson's Law," believes that this is the usual case and that the first sign of decline is the acquisition of "adequate" space.

[8] There were originally three independent hospitals in the hospital complex at Chapel Hill. NCMH was budgeted through the university. Gravely was supported through the Tuberculosis Hospital System, and the South Wing through the Mental Hospital System. Thus, there were three independent budgets and three quite different management styles. These created problems for administrators and opportunities for entrepreneurs.

[9] Dr. Berryhill moved into a trailer after his retirement as Dean, and Dean Taylor's Associate Deans, Chris Fordham and I, also occupied one.



Figure 4. *The retiring Dean, 1964.*

of student advisors, each dealing from admission through graduation with a single student cohort. I agreed to take on the job of supervisor on a part-time basis if he would allow me to organize it the way I wished. He agreed, and this led to a student counseling system which operated effectively until the classes became too large and the student body too heterogeneous.

Final Thoughts about Reece Berryhill

So how shall I conclude my assessment of this remarkable man? Reece Berryhill was highly intelligent, energetic, single-minded and devoted to the University of North Carolina. This devotion provided the focus around which his actions were organized. It also led to clashes with those who were more self-serving. He was an "up-side" person. What I mean is that each of us has either a predominantly "up-side" or a predominantly "down-side" personality, although most of us have a bit of both. The "up-sider" is more concerned about accomplishing his objectives and less concerned about strict observance of rules. The "down-sider" is more concerned about not making administrative errors and less concerned about accomplishing objectives. Business entrepreneurs, artists, and research scientists tend to be "up-siders." Lawyers, accountants, and administrators tend to be "down-siders." My father, who was a businessman, frequently admonished me as a child with this homily: "It's better to be damned for doing something than for doing nothing." Reece Berryhill clearly believed this. Perhaps this was the most basic value which we shared.

SPECIAL ARTICLE

Dr. Berryhill's Third Career, 1964-1978

David S. Citron, M.D.

THESE remarks about Dr. Berryhill are based partly on personal observations and impressions, but mainly on communications from a number of his former students, friends, and associates. Like countless of his other students I considered him a "mentor." In the 1983 Annual Report of the Commonwealth Fund Margaret Mahoney defined a mentor as one who "represents to a young person a commitment to values and modes of behavior that engender a strong sense of personal worth and encourage self-realization." But Dr. Berryhill was a mentor not only for "young persons." His influence on former students prevailed unabated during his entire lifetime. Never having known him intimately, my perspective is limited in comparison with other contributors to this brief history. Nevertheless I hope that I speak for all those whom he influenced far more than he realized.

Dr. Berryhill's plans for a "third career" had begun to germinate long before his resignation from the deanship in 1964. He remembered well that in July 1946 the Committee headed by Dr. William T. Sanger, President of the Medical College of Virginia (already alluded to in Dr. Blythe's biographical sketch) had recommended the establishment of a four-year school of medicine on the Chapel Hill campus, but with a striking proviso, viz:

> "That such a School of Medicine and associated services of the medical school, responsive to the will of the people, be integrated effectively and continuously with a statewide network of hospitals and health centers insofar as these volunteer to cooperate."

From the Charlotte Memorial Hospital and Medical Center, Charlotte 28232.

Dr. Berryhill had repeatedly expressed the concern that he had not fulfilled that expectation and that this was a debt he owed to the state. His sense of mission to meet the needs of the people of North Carolina for health care became an unflagging drive which was to define the remainder of the trajectory of his life. Now he would express it not as architect and leader of a great medical school but as a missionary with a constituency far beyond the boundaries of Chapel Hill. He would serve the community of North Carolina — a community clamoring for more well trained physicians. To fulfill that need — and his promise — he would extend medical education to the community hospitals of North Carolina, challenging the physicians of those communities and the faculty at Chapel Hill to envision the potential of such an initiative. In the process he would experience disappointments and at times frustration; but these moments would be eclipsed by satisfaction in the knowledge that he had played a predominant role in initiating the state's Area Health Education Centers Program, a national model for the decentralization of health education.

In September of 1964, relieved of the tensions of the deanship, he at last took time for a trip abroad with Norma. It was a working holiday, made possible by a Commonwealth Fund Traveling Fellowship. One of his objectives was to study the British National Health Service in order to determine whether this system was relevant to the then current problems of assuring greater availability and accessibility of health care in the United States — problems which were to be exacerbated two years later with the implementation of the Medicare Program.

During his stay in the United Kingdom he had little patience for sightseeing, preferring to delve deeply into the

intricacies of the N.H.S. through interviews with countless physicians, teachers, and policy makers. Curious about the resurgence of general practice in the U.K., he conferred with Dr. John Hunt (later Lord Hunt), First Secretary of the Royal College of General Practitioners. Earlier, during the visits to the Royal College of Physicians, he had been astounded that some of their most prominent members, conservative in the tradition of British physicians, grudgingly accepted the rationale of the "G.P." as a "respectable" and worthy component of the N.H.S.

The experience abroad provided insights which would later be useful to him as he addressed the problem of attracting more physicians in North Carolina to careers in general practice. While abroad Dr. Berryhill was concerned about the state of affairs at the School of Medicine. A new dean had just been appointed but had not yet "settled in"; and two key departmental chairs were yet unfilled. Following a brief trip to Sandinavia, the Berryhills planned a leisurely return to England via Eurail, with stops at points of interest. But Dr. Berryhill eagerly and often restlessly awaited letters from his secretary, Ms. Dunlap, with news of the Medical School. On one occasion during the trip, impatient to return to Scotland to resume his work, he impulsively decided they should forego a planned stopover in Rome. Later remembering that mail might be awaiting him there, he decided that it would be a mistake to change their itinerary; but the stay in Rome was brief — just long enough to get the mail!

In 1965, following his return to Chapel Hill, Dr. Berryhill became the director of the newly created Division of Education and Research in Community Medical Care. The title, though cumbersome, was accurately descriptive of its function, viz: 1) to develop opportunities for the conduct of research relating to community medical care, and 2) to catalyze the establishment of community-based centers of medical education that could relate to the School of Medicine in ways that would be mutually advantageous. Dr. Berryhill had long been openly critical of the quality of existing graduate medical education activities in the state's community hospitals. I first became aware of this when as a naive fourth year student at the Washington University School of Medicine in 1944 I had decided to apply for an internship at Charlotte Memorial Hospital. It was an imposing, newly built structure which would offer, I thought, a rich exposure to common medical problems and supervision by physicians of local renown.

Dr. Berryhill's response to my request for a letter of recommendation was prompt and laconic: No, he would not write such a letter. The teaching program at Charlotte had not yet proved its worth. I should, instead, remain in St. Lous for graduate training in internal medicine at Barnes Hospital. He would be delighted to write a letter to the departmental chairman. Having never had the temerity to question his judgment on a matter relating to medical education — or almost anything else, for that matter — I accepted his wise counsel.

This was the second unwise career decision from which Dr. Berryhill deterred me. The first related to my application for admission to the School of Medicine at Chapel Hill in 1940. A junior student at that time, I was impatient to get on with medical education and opted for medical school admission without prior completion of requirements for the AB degree. Dr. Berryhill was kind but firm. He found my credentials quite adequate, but he felt it necessary to remind me that being Jewish, I might encounter difficulties in transferring from Chapel Hill to a good four year school for completion of my clinical training two years hence. Completion of a fourth year of college, he believed, would obviate the problem. (In that era racial and religious prejudice, both overt and covert, was known to exist among medical school admissions committees.) He left the decision to me, and I gratefully accepted his advice. This encounter with Dr. Berryhill, painful though it was, first evoked my admiration for him. The willingness to discuss a sensitive issue openly, candidly, and with great kindness was to me an early revelation of his greatness and the beginning of an enduring friendship.

In the late 1950s I called Dr. Berryhill again about Charlotte Memorial Hospital. By then I was practicing in Charlotte and at that particular time was charged with assisting in recruiting of interns. There were now, I told him, a large cadre of young, well-trained physicians in Charlotte — many of them alumni of the University — who were eager to participate in the training of house officers. We would appreciate his assistance in attracting some of "his" graduates for training in Charlotte. Without hesitation and with his customary, unemotional forthrightness he replied "No, David, I can't do that. Charlotte Memorial has a bad reputation to overcome." And he was right. My request was premature if not foolish; and as Glenn Wilson[1] recently reminded me, "Dr. Berryhill suffered fools poorly."

In 1962, Charlotte Memorial Hospital, with the support of the Duke Endowment, appointed a Director of Medical Education, Dr. Bryant Galusha, and with this appointment the character of graduate medical education in Charlotte changed. Formerly unstructured and largely experiential, it began to approach the quality of programs in major university teaching programs. And as Galusha acquired additional full-time faculty, appointments to the house staff became highly competitive. Once high educational standards had been assured, Dr. Berryhill enthusiastically offered his assistance. In May 1963, representatives of the School of Medicine met with leaders of the Charlotte programs to discuss a cooperative relationship. An outcome of this meeting was the agreement of the University's Department of Medicine to assist the Charlotte Internal Medicine Residency by allowing residents from Chapel Hill to spend six to twelve months in Charlotte during the third year of training. With the establishment of the Division of Education and Research in Community Medical Care more extensive affiliations followed, not only with Charlotte Memorial, but also with other community hospitals throughout the state.

The evolving orientation of the Division to the North Carolina Area Health Education Centers Program, from 1965 to 1972, was one of uncertainty, experimentation, and struggle. It was perhaps more complex than establishing a new medical school, for no template existed for

[1] Associate Dean for Community Health Sciences, The School of Medicine.

such an organization except in Dr. Berryhill's mind. As early as 1950, referring to North Carolina's "Good Health Program," initiated by the legislature several years earlier, he said" . . . with the active cooperation and participation by the three medical schools in the State, many educational and service opportunities will be available to the medically isolated communities in the State. If adequate funds continue to be supplied our medical personnel, medical service, and hospital shortages should in a relatively short while be alleviated."[2]

Recognizing the educational validity of providing clinical experiences to students and residents which would be highly relevant to and consonant with their eventual practices, and realizing that the resources for clinical teaching in Chapel Hill would be taxed as classes in the medical school were enlarged, he sought to extend education in the health professions to communities throughout the state.

In retrospect I marvel at the abilities of Dr. Berryhill and those who preceded him as deans of the "two year school" to provide effective teaching with faculties which by today's standards would be ludicrously small. But resources at his disposal for conducting the program of the new Division were equally thin.

Dean Isaac Taylor's letter of appointment assured Dr. Berryhill that he would have ". . . a staff consisting of one or more professional assistants and appropriate nonprofessional personnel" and that "the important work of the section (would) eventually require an annual budget in the range of hundreds of thousands of dollars."[3] But the initial budget was meager and the entire professional staff, in addition to Dr. Berryhill, consisted of Dr. Carl Lyle of the Department of Medicine and Dr. Robert Huntley of Preventive Medicine. In retrospect their accomplishments in the early days of the Division were crucial to its survival. Lofty though the concept may have sounded, reaching out to communities to help them improve health care was fraught with difficulties, viz. the sheer size of the state in relation to the modest resources of the Division; the inertia of key faculty members in the School of Medicine, who were occupied with agendas given higher priorities; the uncertainty of future funding of the Division; the ambivalence of community-based physicians toward perceived incursions of their domains by the University; and unrealistic expectations of many communities in relation to their ability to recruit and retain physicians. (The latter problem was succinctly summarized by one of my colleagues, viz. "If a town can't support a first class barber shop it surely won't support a doctor!")

Dr. Berryhill understood fully what opportunities lay ahead, but also what pitfalls. He realized that progress would be made only if leadership could be developed from within the medical community of the state. His genius for sowing the seed of an idea in the minds of others — and deluding them into believing that it was theirs — was of inestimable value. As Bryant Galusha recently reminded me, most people don't care for the "company car" as well as their own. What he meant was that whether it is an idea or an object, pride of "ownership" affects behavior. And Dr. Berryhill was quite willing to forego personal recognition for whatever accomplishments might be achieved in order that community leaders might receive the plaudits — and thereby be more highly motivated. The typical Berryhill approach was "I'm not telling you what do do, but you might want to consider. . . ." As he traveled throughout the state with Lyle, John Payne,[4] Robert Smith,[5] and other close associates in the Division his objective was to identify and reinforce local leadership and delicately channel it, the ultimate goal being the development of local educational programs of high quality. The history of the Division, its relation to the Regional Medical Program, its growth, and its subsequent relationships to the AHEC Program has been written elsewhere.[6] Flourishing under the leadership of its present director, Eugene Mayer, M.D., its presence is felt in each of the 100 counties of North Carolina. Its objectives are articulated with the state's current needs for health professionals. Operating contracts with the four schools of medicine in North Carolina have enabled the establishment of 300 new residency positions in the "primary care" specialties of family practice, internal medicine, pediatrics, and obstetrics/gynecology — many of them in community hospitals geographically remote from the medical school with which they are associated. And programs are conducted in dentistry, pharmacy, public health, nursing, and allied health, providing community-based educational opportunities in these disciplines. A statewide network of library/learning resource centers facilitates access to current information by all health professionals. And a fleet of airplanes facilitates transport of students and instructors to and from the UNC-CH campus and educational sites within the nine regional AHECs.

Although Dr. Berryhill resigned in 1969 from the directorship of the Division and in 1971 from active participation in its activities, his influence remained. Both Robert Smith and Glenn Wilson, who succeeded him, acknowledge that influence. Says Wilson, "When I arrived in Chapel Hill in 1970, knowing very little about the State and its health care problems, he travelled with me, introduced me and said that what I was doing was a good idea. Without his great credibility and his saying 'I'm involved' it might have taken years for AHEC to evolve; in fact without his reputation and good will among physicians in the State it might have failed. His Presbyterian sense of integrity and his commitment to the people of North Carolina made it work. He took an extraordinary chance with a 'kid' from Ohio and gave me his endorsement. I respected him totally; and although we were close friends I could never address him by his first name."

Smith, who also valued Dr. Berryhill's friendship and sponsorship, recalls vividly their many long drives to small communities on behalf of the Division. The hours passed quickly as Dr. Berryhill told endless stories about his

[2] *The News and Observer*, Raleigh, 2/26/50.

[3] I. M. Taylor to Berryhill, December 26, 1967.

[4] Payne is now Deputy Director of the N.C. AHEC.

[5] Smith later became Chairman of the newly-created Department of Family Medicine and is now Chairman of the Department of Family Medicine, University of Cincinnati.

[6] Schnorenberg B.: "The Division of Education and Research in Community Medical Care — 1966-71," (Unpublished papers in archives of the North Carolina AHEC Programs).

ancestral family, his ties with Scotland, the politics of North Carolina, and the early years of the School of Medicine. Dr. Berryhill was at his best as a historian, relating his prodigious memories of the experiences of a lifetime to whatever problems were at hand.

Many honors were bestowed on him during his "second career." Beginning with the O. Max Gardner Award in 1964 (as the member of the consolidated University of North Carolina faculty who had made "the greatest contribution to the welfare of the human race" during that academic year) there followed his appointment as Sarah Graham Kenan Professor in 1968,[7] an honorary doctorate from the University of North Carolina in 1976, the dedication of Berryhill Hall in 1973, and his induction as a Master of the American College of Physicians, the most coveted membership status of that organization.

In 1971 friends and former students in his native Mecklenburg County honored him at a banquet on the occasion of his retirement with announcement by his close friend, Dr. James M. Alexander, of the establishment of the Berryhill-Mecklenburg Medical Student Scholarship. In accordance with Dr. Berryhill's wishes, the scholarships were to be granted on the basis of need, priority being given to residents of the Mecklenburg County area and to American Indians, whom he wished to encourage to study medicine.

When he died, on New Year's Day in 1979, William Friday, President of the University of North Carolina, calling him "one of the University's noble sons," said "His concern was the good health of all citizens, and his dedication was total."

As his friend Cheree Briggs Cleghorn wrote of him in 1973, "Dr. Reece Berryhill is an eloquent testimony to the best we can be."

[7] He was the first faculty member of the School of Medicine to be so honored.

SPECIAL ARTICLE

Dr. Berryhill, My Boss: 1942-1964

Sarah Virginia Dunlap

I first met Dr. Berryhill on the front steps of South Building (the administration building for the University) at seven o'clock in the evening for an interview for the position of secretary in his office. We talked for about forty-five minutes sitting on the steps. He had come back to the campus for this purpose from working in his garden. I was to learn later the importance of gardening in his daily life — flowers, vegetables, shrubs, and trees, and, as he said once, "the opportunity to bury deep in the earth frustrations and even, at times, enemies." Up to his final illness, his garden and plant room were prodigious.

Dr. Berryhill loved the University — more than anyone else I have known — and expressed it by word and deed, through difficult as well as good times. To put it quite simply, Dr. Berryhill *worked* for The University of North Carolina. His vision for the University was high. He understood what should be its goals and ideals and what were its problems.

He had a sense of responsible commitment. Almost from my first week in his office in 1942 I was aware that he was working toward expanding the two-year school into a four-year medical school. He was a consistently busy man who used his time (when he wasn't teaching and administering) to think, write, and contact alumni and friends of the University about his goals for the School of Medicine. Many of the members of the General Assembly and people occupying high positions in state government at that time were former classmates or friends he had known in the University. They were people who loved the University, too, and who were interested in helping it fulfill its obligations to the people of the State.

It would be hard to enumerate the many ways in which Dr. Berryhill served his science, his University, his colleagues, his students, and his friends. Two dominating facets of his personality, to me, were his integrity and his lack of ostentation.

One afternoon while seeing patients at the University Infirmary (an appointment he continued to hold for several years after he became Dean of the School of Medicine), he received a telephone call that his barn was on fire. He did not have his personal automobile at the Infirmary on that day; he had picked up a state car to drive to a nearby town so that he could give a speech for the University early that evening. He would not use the state car to drive the several miles to check on his burning barn. Rather he ran from door to door until he found a doctor who would lend him a car.

When I remember Dr. Berryhill, I remember images:

standing in the hall smoking a cigarette and wearing a white coat that was a little short for him, talking to students or faculty;

sitting at his desk, cigarette in hand, writing a quick, brief note to a student, a faculty member, a friend, an

From the Secretary of the University of North Carolina at Chapel Hill 27514.

acquaintance who needed a word of encouragement or a word of praise or congratulations;

bringing to the girls in the office the first old-fashioned blue hyacinth of the spring from his garden;

returning to the office a day early from vacation with two or three or four legal-size yellow pads completely filled, back and front, with his handwriting;

making daily visits to friends and acquaintances who were patients in the Hospital, whether the janitor or a figure of state or of national importance, usually with a rose or small bouquet of flowers in hand;

delivering remembrances on Christmas Eve to the homes of his office staff;

pacing the floor on a snowy and icy afternoon watching and waiting for the bus (called Black Maria by the students) to return from Durham or McCain where the second-year students had gone for introductory clinical training (before the expansion of the School).

Dr. Berryhill's handwriting, as is true with many physicians, was difficult to read. On one occasion a student in his Physical Diagnosis class brought an examination paper to the office and said he could not read the note Dr. Berryhill had written on it. I read it for him: "Mr. Lewis, I will not waste my time trying to decipher such terrible handwriting. Please see me. W.R.B."

There was no small talk in Dr. Berryhill's conversation; all that he said had a point and it was not an isolated point. Matter-of-factness and evenness was in his voice and written style. He did not pause when he spoke. There were no hems and haws. He spoke as he wrote, always grammatically correct and coherent.

He was a tall man with great dignity — a dignity which characterized everything he did and which, possibly, was why students and young faculty and staff stood in real awe of him — that is until they got to know him. He had a genuine talent to reach out and establish a relationship of appreciation and trust.

Even though his feelings toward individuals were warm, he was a gentleman of the old school in the matter of dignity in his office procedures. One member of his staff, Miss Helen Jane Wettach, was the daughter of two of his closest friends and he, of course, saw her often socially in the Wettach home. In the years she was in his office, however, he never failed once to address her as "Miss Wettach."

The medical students came first with Dr. Berryhill. He knew each student by name wherever and whenever he saw him after his initial meeting. He was not sentimental with students. He never flattered them; he never compromised his standards or his convictions to gain their approbation. He was to the students, as he was to his colleagues, the embodiment of the ideals of learning and civility.

His caring began as they progressed through medical school. If a student wasn't performing well, he was invited to see the Dean in his office. Dr. Berryhill was concerned to find out the reason. A visit with the Dean was a greatly dreaded event by the students; they often left visibly shaken. I learned to know that this, most likely, was due to their great respect for him and their own feeling of having let him down.

In his counseling with students about their postgraduate training and professional life, he was greatly influential in shaping their careers. They never stopped seeking his careful, prudent, and sound advice. One of his real pleasures was keeping in touch with their accomplishments and with their families.

The outstanding faculty assembled at the time of the opening of the four-year school was really Dr. Berryhill's creation. There was a real sense, although he would not wish me to say it, in which that medical school was his, not just its building, but its spirit and quality.

In all that he undertook he was sustained and supported by his wife Norma. As Dr. Berryhill remarked on one occasion, "She did more than anybody." That included entertaining faculty and their families and medical students and their families. During the period of expansion from a two-year to a four-year school, she assisted new faculty in finding housing, welcomed them on the first night in town with flowers and casseroles of hot nourishing food, organized support groups for wives, and on and on.

Dr. Berryhill was a loyal and loving member of his family and a staunch friend. He was devoted to his University, to Chapel Hill, to the State of North Carolina, his country, and his profession. He was, above all, unswervingly loyal to the truth and he was a man of deep religious convictions.

I shall be forever grateful for the privilege of working with him. He greatly influenced any life he touched.

Dean Stuart Bondurant has announced the formation of a committee to plan for a distinguished lecture to be given annually at a convocation of the medical faculty of the University of North Carolina. It will be called the Norma Berryhill Distinguished Lectureship. Contributions to support the lectureship are now being sought. Anyone wishing to may send a contribution to the Norma Berryhill Distinguished Lectureship, Medical Foundation of North Carolina, Inc., MacNider Building, UNC School of Medicine, Chapel Hill 27514.

EDITORIAL

The Development, Justification and Future of a Community Hospital Internal Medicine Training Program

Emile E. Werk, Jr., M.D.

THE development of a successful training program in Internal Medicine in a community hospital is a challenging undertaking. The Area Health Education Center (AHEC) Program of the University of North Carolina and New Hanover Memorial Hospital initiated this effort in Wilmington, North Carolina in 1972. The primary motivating factors were the basic goals of the AHEC program: development of regional educational centers and recruitment of physicians to underserved areas. Several groups participating in this venture had other aspirations. These included hopes for financial support, prestige, enhanced care of indigent patients and improved university-community relations. Formidable opposition existed, fed by the fear of a "university takeover," and worry about a shortage of hospital beds, interference with patient care, and overextension of hospital service facilities. The day-to-day requirements of a training program that include staff and administrative commitment, time, and acceptance of trainees and their needs were not generally appreciated. In the center of this foray was the earnest desire by those immediately responsible to develop the best training program possible. It was clear that working toward this goal was not like a crash program to send an astronaut to the moon with a collection of groups all totally committed to a single, unswerving effort.

Being a part of this challenge from the beginning to the present has provided me with a unique experience lasting over 12 years. Indeed, recent statistics gathered by the Association of Program Directors in Internal Medicine[1] indicate that the average length of service of existing Program Directors was 5 years and the average age was 49 years; the incumbent is near 2 standard deviations on both counts.

Progress has been made. As the report of Ungaro and Gonzalez in this issue of the *Journal* documents, 23 trainees have completed 3 years of internal medicine training at New Hanover Memorial Hospital. Fifteen of these physicians are practicing in North Carolina, almost half in small towns. These physicians are highly regarded in their respective communities. Thus, it appears that a degree of success has been achieved. What has this depended upon? A circuitous course of compromise, coupled with a strong sense of determination and a spirit of mutual respect have all been involved. Strong support from the University of North Carolina, the AHEC administration, the hospital administration and the talented local full-time faculty have all been vital. But the most central factor of all has been the unrelenting support of our community's internal medicine practitioners. A small number of actively teaching clinical faculty has steadily increased to form an enthusiastic and sizable group of subspecialists and generalists. Many are younger physicians who have been attracted to the area by the desire to participate in teaching as well as to enjoy a sophisticated medical environment in a coastal location.

What about the quality of trainees in such a young program? Certainly this is an important question. Competition among training programs for top notch medical school graduates is keen. It might be said that given the requirements and inspection process of the Residency Review Committee in Internal Medicine and the clinical skills demands set forth by the American Board of Internal Medicine, most programs today are of high quality. Recruitment has been and undoubtedly will continue to be one of the major challenges in community hospital programs.

Is the community hospital truly justified in training physicians in internal medicine in comparison with the highly sophisticated university medical center? Having closely observed both sides, my biased response is an emphatic "yes." Community program trainees acquire superior clinical skills that enable them to deal with common disorders, decision making, and cost benefit analysis. They have a unique opportunity to develop strong humanistic traits. It is my impression that the cost of medical care provided to our housestaff patients is not greatly different from that of private patients in this hospital. This is in contrast to the considerable difference found in a recently published Stanford study.[2] Moreover it must be emphasized that many clinical practitioners in community hospitals have the ability and capacity to be exceptional teachers and role models. Our residents have initiated the E. Thomas Marshburn award which will be given yearly to the third year resident who best exhibits the "outstanding qualities of an internist as exemplified by Dr. E. Thomas Marshburn." A practicing internist, Dr. Marshburn has been an active, popular teacher since the program was

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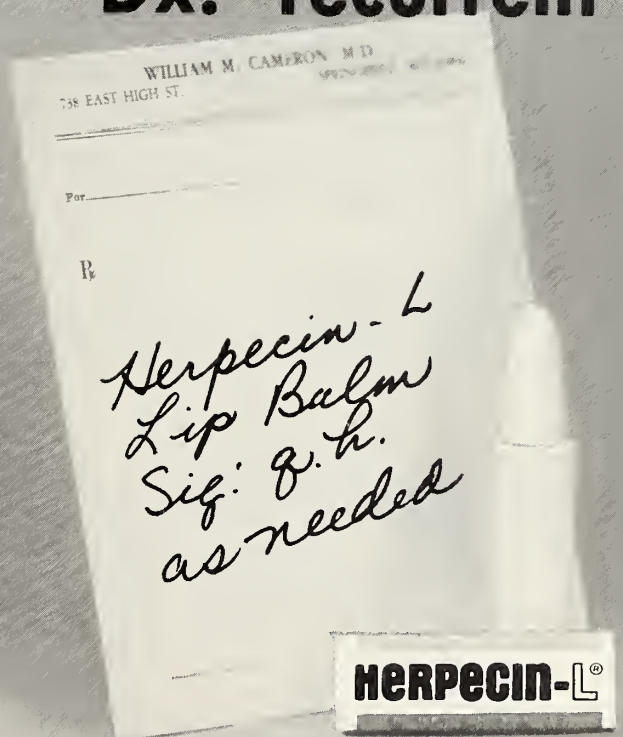
started. He is a prime example of a community teaching resource that could not be utilized if there was no teaching program.

The biggest challenge of all probably lies ahead. Can community hospital training programs survive in the face of physician surplus, the increased cost of health care, federal regulations and the financial drain on community hospitals? Those of us who have seen the advantages of a community hospital program become more and more apparent would hope so. The collapse of such programs would be most unfortunate. The money and effort already expended to develop them to their current level would be lost. In addition a valuable resource for training highly skilled clinicians for North Carolina would be missing.

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Isolated ACTH Deficiency; a Not-so-Rare Syndrome, with Variable Manifestations

Jorge J. Gonzalez, M.D. and Emile E. Werk, Jr., M.D.

• *Four patients are presented with isolated adrenocorticotrophin deficiency and a variety of symptoms.*

SINCE the description of the first case of isolated adrenocorticotrophin (ACTH) deficiency by Steinberg et al in 1954,[1] another fifty or so cases have been added to the world's literature. As its name implies, this syndrome is characterized by deficient ACTH secretion in the presence of an otherwise normal hypothalamus pituitary unit.

Clinically isolated ACTH deficiency appears more often between the fourth and sixth decade. The symptoms are nonspecific, and the clinical presentation may be quite variable. In sharp contrast with classical Addison's disease, these patients are rarely pigmented and lack the "telltale" hyperkalemia so chacteristic of the mineralocorticoid deficiency of Addison's disease. In addition, patients with this syndrome appear to be more resistant to stress than patients with Addison's disease. The higher resistance to stress could be related to the preservation of the mineralocorticoid function and/or the higher residual glucocorticoid secreting capacity present in these patients.

These characteristics of this syndrome make it difficult to recognize and it is not rare for these patients to have several previous hospitalizations before the definite diagnosis is made. We observed four cases of isolated ACTH deficiency over the last few years. We believe that they demonstrate the heterogeneity of symptoms and the different kinds of presentation of this syndrome.

Case 1

D.M., a 74-year-old black man, was admitted to the hospital for seizures which had started several months previously and increased in frequency. There was no history of trauma. He had been followed in the medical outpatient department for an "aplastic anemia" thought to be related to insecticide exposure. On physical exam his blood pressure was 70/40 and he had a normal pulse and temperature. He appeared thin, wasted, and apathetic. There was no increased pigmentation. Genitalia and sexual hair were normal and the prostate gland was slightly enlarged. Pertinent laboratory findings included a hemoglobin of 11.2 with 2800 white cells and normal differential. Blood glucose was 57 mg/dl, urea nitrogen 6 mg/dl, serum sodium 118 mEq/L, potassium 4.4 mEq/L, chloride 81 mEq/L, CO_2 25 mEq/L, creatinine 1.1 mg/dl, and cholesterol 155 mg/dl.

The patient was given intravenous fluids and diphenylhydantoin and an endocrine evaluation was instituted. He remained weak and drowsy. Eight days later he became stuporous and his blood sugar was 15 mg/dl. Intravenous hydrocortisone was started, followed by maintenance oral hydrocortisone. Marked improvement occurred. Levels of serum electrolytes and blood sugar became normal. The endocrine tests prior to steroid treatment showed zero cortisol levels with one ACTH level of 56 pg/ml (normal <100). After intramuscular Cortrosyn, plasma cortisol remained zero and aldosterone increased slightly from 2 to 3 ng/dl. An upright plasma renin activity level was 0.3 ng/ml/hr. Levels of thyroxine, sleep stimulated growth hormone, LH and testosterone were normal. Subsequently he was followed in the outpatient department with continued gain in strength and weight. Blood pressure increased to hypertensive levels requiring mild diuretic therapy despite low maintenance dose of prednisone. Six months later he was admitted for a three day ACTH stimulation test. During the readmission evaluation he was given aqueous ACTH 40 U intravenously over 8 hours for 3 days. Plasma cortisol concentration increased stepwise to 12 μg/dl, urinary 17-hydroxycorticosteroids to 3.7 mg/24 hr, and free urinary cortisol to 34 μg/24 hr. Plasma aldosterone was 11 ng/dl and PRA was 13 ng/ml/hr after furosemide administration. Radiological studies of the pituitary were normal. He has continued to do well on prednisone replacement. His hematological indexes normalized after replacement therapy.

Case 2

W.W., a 48-year-old white man, was admitted to the hospital in October 1972 because of progressive weakness and dizziness. He stated that he had been sick on and off for three years. In 1969 he had a subtotal gastrectomy at another hospital presumably for peptic ulcer disease. Since then he had repeated episodes of nausea, vomiting, and diarrhea, requiring several hospital admissions. In 1970 at another hospital he was said to have unexplained "hyponatremia" and weight loss. In 1971 and early 1972 he was admitted to this hospital with the diagnoses of 1) dumping syndrome, 2) psychogenic food intolerance, 3) broncho-

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pneumonia, and 4) positive serology for syphilis, treated. During the 1972 hospital admission, a serum sodium of 105 and potassium of 5.1 mEq/L were noted and treated with intravenous saline.

Physical exam revealed a poorly nourished white man appearing very weak and older than his stated age. Blood pressure was 110/60 supine and the systolic pressure with a pulse pressure of 0 on standing decreased to 90. Pulse was 100. There was no increased pigmentation. Genitalia and sexual hair were normal.

Laboratory tests showed a hemoglobin of 10.1 and 5300 white blood cells. Serum sodium was 116 and potassium 5.3 mEq/L. Chest x-ray showed pleural thickening and emphysematous bleb formation.

Hypopituitarism was suspected and the following endocrine tests were performed: Serum thyroxine 7.3 μg/dl (normal: 3.3-8.9), plasma renin activity upright 1.18 ng/ml/hr (normal: 1.0-5.0), plasma cortisol at 8 a.m. 12 μg/dl (normal: 7.0-23.0), and at 8 p.m. 10 μg/dl (normal: 5.0-15.0). The serum cortisol increased from 9 μg/dl to 42 mg/dl after 8 hours of ACTH infusion. An insulin tolerance test (0.1 μ/kg) (table 1) showed sustained hypoglycemia with poor responsiveness in cortisol but a rise in the level of growth hormone. Skull x-ray was normal.

The patient was treated with 12.5 mg cortisone acetate twice daily and followed in the outpatient clinic. There was a dramatic improvement in strength and appetite. Weight increased from 93 to 105 lb over the next several weeks. The serum sodium concentration was 141 and potassium 4.5 mEq/L. Additional laboratory evaluation during his follow-up revealed a testosterone level of 1000 ng/dl and a normal prolactin level.

Approximately 6 years after the diagnosis, the patient developed a macrocytic anemia, with a low vitamin B_{12} level, a positive Schillings test, positive anti-parietal cell antibodies and negative anti-intrinsic factor antibodies. An upper GI series revealed a 60% gastric resection with a Billroth II procedure. Gastric biopsy showed atrophic gastritis with absent parietal and chief cells. It was not possible to differentiate between B_{12} deficiency secondary to gastrectomy or true pernicious anemia. The patient was treated with monthly shots of vitamin B_{12} and his blood counts became normal.

Case 3

M.A., a 49-year-old white woman, was referred January 1982 to the endocrine clinic by her local practitioner because of hypothyroidism. She felt that she had gradual weakness for as long as 15 years which became much worse during the previous year and was accompanied by fatigue, cold intolerance, deepening voice, axillary hair loss and menstrual irregularity. She had had five uneventful pregnancies, the last 15 years previously. All five children were living and well. A unilateral ovary and tube had been removed in 1968 and appendectomy performed in 1959. There was no family history of autoimmune disease. Her mother had breast cancer.

The physical examination revealed a weight of 162 lb, a height of 63″, and a normal pulse and blood pressure. The patient appeared pale, puffy and sluggish. The skin was dry and thickened without pigmentation. Axillary hair was sparse. The thyroid was not felt. Deep reflexes showed delayed relaxation.

Thyroid function tests revealed a T_3 resin uptake of 0.68 (normal: 0.80-1.20), a T_4 of 4.7 μg/dl (normal: 4-12), a free thyroxine index (FTI) of 3.7 (normal: 5-12) and TSH level of 16 μU/ml (normal: <5). Antithyroglobulin antibodies were positive with a titre of 1600 and microsomal antibodies were negative.

The patient was placed on increasing dosage of l-thyroxine. Over the next several weeks she noted minimal improvement in energy and decreased constipation but as the dosage of l-thyroxine was increased above 0.075 mg/day she felt even weaker. Normal levels of thyroxine, 8.4 μg/dl, TSH 4.5 μU/ml, sodium 143 mEq/L, and potassium 4.2 mEq/L were noted. A morning level of cortisol was low, 5.3 μg/dl (normal: 6-20). We planned to evaluate the patient further for adrenal insufficiency but she did not return for 6 months.

At that time she stated she had discontinued the l-thyroxine and felt persistently weak. Excessive menstrual bleeding had occurred. She appeared again pale, puffy and weak. She was admitted to the hospital for further endocrine evaluation. Routine laboratory tests and serum electrolytes were normal. The patient was taking l-thyroxine 0.05 mg daily when these tests were done. A short ACTH stimulation test showed the following values.

	Basal	30 Minutes after Cortrosyn
ACTH (pg/ml-	<20	
Cortisol (μg/dl)	0.5	4.7
Aldosterone (ng/dl)	6	24

An insulin stimulation test and a metyrapone test were then performed (see table 2). The ACTH, cortisol and deoxycortisol responses confirmed a deficiency of ACTH. The growth hormone response to insulin hypoglycemia was flat. Retesting of the growth hormone axis with other stimulatory agents is pending. Estradiol, FSH, LH levels showed normal premenopausal concentrations. A CT scan of the head and polytomograms of the pituitary fossa were normal.

The patient was discharged from the hospital to take prednisone 5 mg in the morning and 2.5 mg in the evening, and l-thyroxine 0.05 mg each morning. Follow-up in the outpatient department revealed that the patient felt much

Table 1
Insulin Tolerance Test (0.1μ/kg IV) in Patient 2

	Glucose (mg/dl)	Cortisol (μg/dl)	Growth Hormone (ng/dl)
Fasting	75	6	2
30′	30	8	2
60′	26	8	3.4
90′	27	7	3.7
120′	31	7	4.6

Table 2
Insulin Tolerance, TRH Stimulation and Metyrapone Test Results in Patient 3

Time	Glucose (mg/dl)	Cortisol (μg/dl)	Prolactin (ng/ml)	ACTH (pg/ml)	TSH (μU/ml)	GH (ng/dl)
	Insulin Tolerance (0.1 μ/kg IV) and TRH Stimulation Test (200 μg IV)					
0	76	0.9	14	< 20	7.7	1
30	154*	1.2	61	< 20	27.3	1
60	111	1.1	44		18.6	1
90	73	1.0	29	< 20	16.0	1
			Metyrapone Test			
Metyrapone, 2 gr PO at midnight 8 a.m. ACTH < 20 (normal: 180-900 pg/ml) 8 a.m. ACTH deoxycortisol 0.4 μg/dl (normal: 7-22 μg/dl)						

* 25 ml of D50/W given intravenously due to severe hypoglycemic symptoms

improved. Her weakness was ameliorated. Over several weeks the prednisone dosage was decreased to 4 mg in the morning and 1 mg in the evening, and she was able to tolerate 0.1 mg l-thyroxine daily. Menses became regular at 4 week intervals.

Case 4

This 25-year-old black woman was admitted to the hospital with hypotension, fever, and lethargy. She had taken oral penicillin during the previous 48 hours. She had complained of sore throat, fever, and headache. She had been taking INH for 6 months for a recent PPD conversion. Her menstrual periods had been normal. Her temperature was 102.5°F. Stiffness of the neck and a positive Brudzinski's sign were noted. No other abnormalities were found.

CT scan of the head was normal. A lumbar puncture showed a protein of 56 mg/dl with 3 white cells and a glucose of 26 mg/dl. Smear and cultures of the CSF were negative. Admission laboratory tests showed a blood sugar of 60 mg/dl. Serum electrolyte levels were normal, with the exception of a bicarbonate of 17 mEq/L. Her serum creatinine was 1.6 mg/dl. A cortisol level was 1.7 μg/dl with a simultaneous ACTH level of less than 20 pg/ml. The patient was treated with a broad spectrum antibiotic and given methyl prednisolone.

She responded well to therapy. Glucocorticoids were discontinued after 24 hours, and 6 days later she continued to have a low serum cortisol with undetectable ACTH level. Urinary free cortisol was less than 2 μg/24 hr. Thyroid antimicrosomal and antithyroglobulin antibodies were negative.

Detailed endocrinological evaluation of this patient is being published in detail elsewhere.[2]

This evaluation confirmed the diagnosis of isolated ACTH deficiency. The patient was started on glucocorticoid replacement and has done very well since then.

Discussion

In their extensive review, Stacpoole et al[3] found that hypoglycemia was the most common clinical finding reported in these patients (56% of cases). Hyponatremia on the other hand was the least frequent clinical manifestation encountered. The frequency of weight loss, hypotension, anemia, weakness, nausea and vomiting, and inability to excrete a water load was found to be between the above mentioned extremes. In contrast to this distribution, two of the four patients presented here had hyponatremia and there was only one episode of spontaneous hypoglycemia. One patient had mild hyperkalemia. Hypotension was seen in three of the four patients.

Patient 3 had a flat response of growth hormone to hypoglycemia. This suggests a "combined deficiency" rather than isolated ACTH deficiency. However, it is well known that a small fraction of normal people fail to demonstrate stimulation of growth hormone with hypoglycemia.[4] The definitive diagnosis of growth hormone deficiency requires at least two provocative tests to evaluate growth hormone secretion.

The clinical heterogeneity of the isolated ACTH syndrome might be accounted for by differences in underlying cause. ACTH deficiency can originate within the pituitary or in the hypothalamus or, at least in theory, in higher encephalic centers. The fact that some patients with isolated ACTH deficiency respond to vasopressin with an increase in ACTH[3] suggests that a fraction of these patients have an intact pituitary. It is likely that with the use of the newly isolated corticotropin releasing factor (CRF) a better delineation of the origin of the syndrome will be possible. It has been reported recently that the CRF stimulation test holds promise in distinguishing a failure at the level of the pituitary from one that originates in the hypothalamus.[5] Unfortunately, pathological studies in this entity are practically nonexistent.

The coexistence of primary autoimmune hypothyroidism with isolated ACTH deficiency has been reported previously.[6] One of the patients in this series presented with the classical clinical situation of hypothyroidism which gets worse after thyroid replacement, and ACTH deficiency was ultimately diagnosed. Conventional endocrine wisdom has taught us to suspect coexisting Addison's disease in these patients (Schmidt's syndrome). The patient presented here and the similar patients reported in the past demonstrate that in clinical medicine exceptions to the rule are common.

The coexistence of Hashimoto's thyroiditis with isolated ACTH deficiency, and the pathologic findings of both

lymphoid hypophysitis and lymphoid thyroiditis in one previously reported patient[7] suggest an autoimmune mechanism for some of the cases of ACTH deficiency. In patient 2 it was impossible to differentiate between true pernicious anemia and anemia secondary to gastrectomy. In any case, it appears possible that isolated ACTH deficiency due to lymphoid hypophysitis will add in the future to the evergrowing list of autoimmune polyglandular failure syndromes.

We think that isolated ACTH deficiency may be more common than reported up to now, and we hope that this report will stimulate the detection of new cases in our state.

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SCIENTIFIC ARTICLE

Hereditary Angioedema as a Cause for the Non-Surgical Acute Abdomen

John D. Hunter, M.D.

- *Severe abdominal pain can be the only presenting feature of hereditary angioedema.*

ACUTE severe abdominal pain is a major challenge in any medical practice. This is particularly true when a previously healthy young person is in considerable distress without a history, physical sign, or laboratory abnormality that points to a surgical problem.[1] What should be included in the non-surgical evaluation? When are laboratory tests cost-effective to diagnose the rarer medical causes of abdominal pain? When is the "organic" workup complete and when should psychiatric evaluation begin?

Hereditary angioedema is a medical cause, albeit uncommon, of acute, severe abdominal pain.[2, 3] This autosomal dominant deficiency of C_1 esterase inhibitor ($\overline{C}_1INH$) in the complement cascade usually presents with painless nonurticarial swelling, sometimes causing fatal laryngeal edema. However, striking abdominal discomfort can be the sole initial feature.[4]

A patient with hereditary angioedema, therefore, serves as an excellent example of a rare medical cause of the non-surgical acute abdomen. With a reasonable index of suspicion and careful clinical analysis, extensive diagnostic radiologic and invasive procedures, including laparotomy, can be avoided.

Case Report

A 20-year-old white married woman was admitted for the second time in a month for acute severe abdominal pain. Four weeks previously she had developed mid-abdominal sharp grabbing pains and had been treated for presumed pelvic inflammatory disease. However, within 48 hours she was hospitalized by her gynecologist with persistent pain. She had no fever and a relatively normal abdominal exam, but there was a suggestion of right-sided tenderness with fullness in that area on pelvic exam. X-ray of chest and abdomen and blood studies were all normal, with the exception of a very minimally elevated SGOT. She underwent diagnostic laparoscopy which suggested a ruptured corpus luteum cyst. Her pain subsided after about 96 hours.

She remained pain-free for three weeks but was hospitalized again with the same mid-abdominal sharp grabbing pain, occurring suddenly, unassociated with bowel or bladder symptoms, nausea, vomiting, fever, chills or bleeding. She was quite uncomfortable, but had minimal non-focal guarding. The pain subsided again in four days.

On this occasion, however, she had puffiness about the cheeks and forearms. Though the patient had no prior history of abdominal pains, she did relate intermittent nonspecific puffiness of the face and extremities. She denied previous cardiac, renal or liver problems, or illicit drug use. She was taking no medications other than Tylenol, and no contraceptive pills. She drank no alcohol. There was no allergic history and she denied emotional stress.

More careful history revealed that several family members had multiple abdominal surgical procedures, especially cholecystectomy, but often with apparently minimal pathological findings, and with persistent pain after surgery.

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Table 1
Clinical Characteristics of Hereditary Angioedema Attacks in 28 Patients

	Patients %
Precipitating factors	
Trauma	54
Anxiety or stress	43
Signs and symptoms	
Peripheral angioedema	96
Facial angioedema	85
Pharyngeal angioedema	64
Recurrent abdominal	
Pain	93
Nausea or vomiting, or both	88
Diarrhea	22
Rash	26
Most common disease manifestation	
Peripheral angioedema	79
Abdominal pain	21

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Subsequent evaluation revealed normal blood counts, urinalysis, serum amylase, and chemical screen. An upper GI series, small bowel x-ray, oral cholecystogram, barium enema, gall bladder and pancreatic ultrasonography and intravenous pyelogram were normal. Urinary drug screen and Watson-Schwartz urinary tests were negative. However a low C4 level, elevated complement decay rate of 85% (CH_{50} titer after incubation in a low ionic strength buffer), and $\overline{C}_1$INH level of 5 mg% (20% of normal, by anti-serum method) were discovered.

The patient has now been pain-free for over a year on no specific therapy. Family screening subsequently revealed her mother to have a similar history of abdominal pains and swelling and to have $\overline{C}_1$INH deficiency. Further family screening is pending.

Discussion

Hereditary angioedema is a rare but important clinical entity. Death occurs in 14-30% of patients, who are often young, usually from acute laryngeal edema and obstruction.[2, 3, 5] Attacks are largely preventable once the diagnosis is made. But in a study of 30 patients from the National Institute of Health it was found that the median duration of symptoms before the diagnosis was established was 21 years.[2]

Certain clinical clues should raise the physician's index of suspicion (table 1).[2] Over 85% of patients relate a history of recurrent unexplained bouts of painless, nonpitting, nonurticarial, nonpruritic edema of the face or extremities. Since inheritance is autosomal dominant with variable penetrance, a family history of compatible symptoms is found in 75% of patients. Frequently this includes repeated surgical operations such as cholecystectomy, appendectomy and hysterectomy, followed by recurrent abdominal pain. Many patients are labeled with functional bowel symptoms or neurosis.

The typical patient is a white young person (90%) of either sex (two-thirds are symptomatic before age 13 with

Table 2
Medical Conditions Causing the Acute Abdomen

Familial Metabolic
Acute intermittent porphyria
Familial hyperlipoproteinemia
Familial mediterranean fever
Hereditary angioneurotic edema
Hemochromatosis
Endocrine
Diabetic ketoacidosis
Addisonian crises
Hyperthyroidism
? Hyperparathyroidism
Inflammatory
Noninfectious
Pancreatitis
Inflammatory bowel disease
Infectious
Enteric infections (typhoid, shigellosis, staphyloccal enterocolitis, etc.)
Primary peritonitis (pneumococcal tuberculosis)
Pelvic inflammatory disease
Hepatitis (viral, Q fever, alcoholic)
Infectious mononucleosis
Herpes zoster
Pyelonephritis
Prostatitis
Nonspecific jejunitis (?)
Mesenteric adenitis (?)
Referred Pain
Thoracic
Pericarditis
Pleuritis
Acute myocardial infarction
Myocarditis
Abdominal wall (rectus sheath hematoma)
Retroperitoneal
Renal colic
Renal infarction
Neurologic
Tabes dorsalis
Nerve root compression
Glaucoma
Pelvic
Mittelschmerz
Endometriosis
Abdominal migraine
Abdominal epilepsy
Collagen Hypersensitivity
Acute rheumatic fever
Systemic lupus erythematosus
Polyarteritis nodosa
Henoch-Schoenlein purpura
Allergy (?)
Drug-Toxin
Heavy metals (lead, arsenic, mercury)
Mushroom
Staphylococcus toxin
Arachnoidism
Anticoagulants (especially coumadin)
Narcotic withdrawal
Hematologic
Sickle cell anemia
Acute hemolytic states
Leukemia
Clotting abnormalities

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an overall range of 10 to 72 years).[2, 3] Attacks are precipitated by trauma, dental care, or physical or emotional stress in 54% of cases. Menstruation and oral contraceptives may induce attacks, but pregnancy and delivery have been associated with a decreased incidence. Patients obviously need to be prepared carefully for surgery or dental manipulations.

Recurrent abdominal pains occur in 93% of patients, are the presenting feature in 52%, and the major manifestations in 21%.[2, 3] Discomfort is usually moderate, vague, and diffuse without peritoneal signs, but intestinal obstruction and hypotension can occur. Nausea, vomiting and diarrhea are common, but fever is not. Submucosal edema of the bowel wall can yield a "stacked coin" appearance on x-ray.

Though even mild trauma can be a precipitating factor, the pain comes and leaves mysteriously, usually within 24 to 48 hours (range 4 hours to 1 week). Often several x-rays, including arteriograms, are ordered, and the patient sometimes is subjected to needless laparotomy. A normal CBC, absence of fever, and lack of localizing abdominal signs should allow conservative observation instead of surgery.

Deficiency of the inactivator of the first component of complement $\overline{C}_1$INH affects the kallikrein and fibrinolytic plasma symptoms as well as the complement cascade.[6] Thus these patients have played an important role in understanding the enzyme activities of these complicated systems. Nonetheless the pathophysiology of the episodic angioedema is not understood. It is known that during an attack of hereditary angioedema, unbridled C_1 persistently consumes C_2 and C_4 substrates which virtually disappear, while terminal components of the complement pathway remain in normal amounts. Both C_2 and C_4 can return to normal levels between episodic attacks, though C_4 usually remains diminished.[7]

A reasonable initial screen for hereditary angioedema is a C_4 level. Confirmation should include a protein $\overline{C}_1$INH level which is usually less than 30% normal. About 20% of patients will have normal $\overline{C}_1$INH *protein* levels, but abnormal *functional* $\overline{C}_1$INH levels in assays of enzyme activity. Systemic lupus erythematosus can also present with angioedema and a low C4 level and must be differentiated. Rarely an "acquired" $\overline{C}_1$INH deficiency exists in certain lymphoma patients.

Treatment consists of preventing attacks by stress modification and chronic androgen administration. The androgen derivative Danazol has been favored because it has fewer side effects than other androgens.[8] Danazol should be administered to patients with hereditary angioedema for at least 10 days before surgical operations or routine dental care. Fresh frozen plasma can also be given preoperatively to increase $\overline{C}_1$INH and C_4 levels. Antifibrinolytic agents have also been used as chronic preventive therapy.

No chemical maneuvers can shorten an ongoing acute attack. Tracheostomy is indicated if there is a sign of impending upper airway obstruction, including dysphasia or change in voice. Treatment of acute abdominal pain is symptomatic and supportive. Unnecessary tests should be avoided.

"Non-Surgical" Acute Abdomen

Certain important historical and physical clues should suggest the medical cause of an acute abdomen from the long list of possibilities shown in table 2. Nearly half the diagnoses are quite uncommon.[1] Nevertheless there are situations in which it is important to consider tests such as a thyroid panel, lipid panel, Watson-Schwartz urine test, heavy metal screen, drug urinary screen, stool white cells and red cells, $\overline{C}_1$INH assay, FANA, hemoglobin electrophoresis, etc.

The question of the cost effectiveness of an extensive work-up for uncommon disorders is a difficult one. Taking the time to listen to the patient and family and to do repeated physical exams should provide appropriate indications for individual tests. Acute abdominal pain is not an emergency, once bleeding and surgical causes have been ruled out. Careful observation could prevent costly, ineffective and unnecessary diagnostic x-rays, or even major surgery.

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SCIENTIFIC ARTICLE

Porphyria Cutanea Tarda in Association with Multiple Myeloma

Jon M. Maier, M.D. and Peter C. Ungaro, M.D.

• *Report of a patient with the previously undocumented association of porphyria cutanea tarda with multiple myeloma.*

PORPHYRIA cutanea tarda is the most common clinical abnormality of porphyrin metabolism.[1] The disease is characterized by hypertrichosis, hyperpigmentation, vesiculobullous dermatosis in sun exposed areas, and red-wine colored urine. It has occurred secondary to a variety of drugs, toxins, and diseases including various neoplasms. However, it has not been previously reported in association with multiple myeloma.

Report of a Case

T. H., a 65-year-old white female, presented with complaints of weakness and abdominal pain. She had been treated previously with methychlothiazide and deserpidine for hypertension, and she also had taken an iron-containing vitamin pill for six years for an "anemia." There was no history of ethanol ingestion, tobacco abuse, or other drug use. She denied exposure to hexachlorobenzene or other polychlorinated phenols. There was no family history of porphyria cutanea tarda. On physical exam she was obese and had hepatomegaly. Her complete blood count was remarkable for a normochromic normocytic anemia with a hemoglobin of 9.5 g/dl. The serum iron was 93 mg/dl with a TIBC of 240 mg/dl. Immunoelectrophoresis showed an IgG lambda monoclonal spike. A bone marrow aspirate and biopsy showed plasma cell infiltration.

Although therapy with melphalan and prednisone was initiated, the patient decided not to take additional cytotoxic therapy after the second four-day cycle, and it was ten months before she returned for further evaluation. She stated that her urine had been amber in color for the prior four months. She had persistent hepatomegaly, vesiculobullous dermatosis on the hands (figure 1) and face, hypertrichosis and hyperpigmentation on sun-exposed areas, and red-wine colored urine. A liver biopsy showed marked hepatic siderosis, and mild fibrosis. No mass lesion was seen on liver-spleen scan and serum ferritin was 1400 ng/ml. No serum antinuclear antibody was detected and the Watson-Schwartz test was negative. On a 24-hour urine collection uroporphyrins were 1200 mcg and coproporphyrins were 480 mcg. Analysis of another sample by high pressure liquid chromatography demonstrated the predominant porphyrins to be uroporphyrin and 7-carboxyl porphyrins. Fecal analysis showed a coproporphyrin level of 46 mcg/g and a uroporphyrin of 12 mcg/g. Erythrocyte uroporphyrinogen decarboxylase was normal.

The patient was kept away from sunlight and the skin lesions cleared over a period of two weeks. She refused chloroquine therapy and further treatment for her myeloma. Her anemia precluded phlebotomies.

Discussion

Several investigators have reported the association of porphyria cutanea tarda with tumors, primarily hepatic neoplasms including hepatic adenomas.[1] Resolution of the histological and biochemical evidence of porphyria cutanea tarda following removal of a tumor has been described.[2] Chronic myelocytic leukemia is the only hematologic neoplasm described with porphyria cutanea tarda to date.[3] The patient with chronic myelocytic leukemia, like ours, presented with signs of the underlying neoplasm and was treated with an alkylating agent, busulfan. Months later both that patient and our patient developed characteristic porphyria cutanea tarda. The patient with chronic myelocytic leukemia had hepatic leukemic infiltrates while ours had a liver biopsy that was remarkable primarily for the presence of siderosis. Increased hepatic iron stores are characteristically found in porphyria cutanea tarda,[4] and our patient's hepatic siderosis was an expected manifestation.

This paper reports the previously unreported association of porphyria cutanea tarda and multiple myeloma. It is possible that the simultaneous occurrence of these two disease processes was coincidental, but it is also quite possible that the myeloma may have induced the porphyria cutanea tarda. There are apparently two groups of patients with porphyria cutanea tarda in addition to the patients with hepatic neoplasms. One group has an inherited defect in uroporphyrinogen decarboxylase in both erythrocytes and hepatic cells.[5] The clinical syndrome becomes manifest when these patients are exposed to drugs or other chemicals that affect the porphyrin metabolic pathway. The other group consists of patients who have normal uroporphyrinogen decarboxylase levels in their erythrocytes. They seem to have selectively inhibited hepatic enzymatic activity from exposure to those few chemicals that are capable of producing this effect. It is possible that some of these

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Figure 1. *Patient's vesiculobullous dermatosis.*

patients also have an inherited susceptibility due to some hepatic abnormality, but this has not been established. Our patient had normal erythrocyte enzyme levels and no history of exposure to chemicals associated with enzyme inhibition. It is possible that our patient's myeloma synthesized a substance that resulted in hepatic injury which caused a disruption of porphyrin metabolism. Further clinical observations in additional patients might clarify this issue.

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Chronic Myelogenous Leukemia Presenting Clinically As Diabetes Insipidus

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• *Report of a patient in whom diabetes insipidus was the earliest clinical manifestation of chronic myelogenous leukemia.*

DIABETES insipidus is a rare complication of leukemia.[1] A careful review of the literature reported in 1971 identified 21 cases, of which only five were associated with chronic myelogenous leukemia.[2] Since that time several additional cases have been reported,[3] but most of these have been associated with acute leukemia. In the great majority of cases, the diabetes insipidus has become manifest after the diagnosis of leukemia has already been established. This report is about a case in which diabetes insipidus was the initial manifestation of chronic myelogenous leukemia. Possible mechanisms responsible for this presentation and therapeutic implications are emphasized.

Report of a Case

S.W. was referred to the Internal Medicine Service at New Hanover Memorial Hospital in January 1977 when she was 50 years of age. She had been in her usual state of good health until approximately two months prior to admission when she noted the gradual onset of increased thirst and water drinking associated with increased urinary volume and frequency. When she was evaluated by a neurologist a month prior to admission, she complained of lethargy related to sleep interruptions from having to get up every hour during the night to urinate. No neurological abnormality was detected then or subsequently.

On admission physical examination blood pressure was 164/94 and there was no lymphadenopathy or organomegaly. A complete blood count was as follows: hemoglobin 14.0 gm%, platelets 90,000, WBCs 35,100 with 37% polys, 13% bands, 5% metamyelocytes, 2% myelocytes, 32% monocytes, 1% basophils and 10% lymphocytes. Subsequent blood counts are indicated in table 1. Leukocyte alkaline phosphatase was normal. The vitamin B_{12} level was 1900 pg/ml. Bone marrow was hypercellular with a myeloid:erythroid ratio of 6.3:1. A subsequent bone marrow cytogenetic study was negative for the Philadelphia chromosome. No splenomegaly was found on liver-spleen scan.

Serum and urine osmolarities are shown in table 2. These are compatible with diabetes insipidus. There was a prompt rise in urine osmolarity with intramuscular administration of 10 units of vasopressin. Brain scan was within normal limits and skull films showed a normal pituitary fossa. The patient was discharged on lypressin nasal spray; no antileukemic therapy was begun.

In spite of the fact that the polyuria and polydipsia were well controlled, the patient was anxious for additional evaluation and was admitted to another hospital in June

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Table 1
Treatment Profile

Date	Hgb	WBC × 10^3	Plts × 10^3	Therapy
Jan. 27, 1977	14.0	35.0	90	No treatment
June 30, 1978	12.2	51.8	102	Melphalan 4 mg daily started
July 28, 1978	12.7	13.6	86	Melphalan continued
Aug. 11, 1978	13.0	15.7	38	Treatment stopped (thrombocytopenia)
Oct. 10, 1978	13.4	7.4	41	No treatment
Nov. 17, 1978	12.6	16.3	65	No treatment
Feb. 2, 1979	13.3	29.9	77	Melphalan 2 mg every second day started
Mar. 16, 1979	12.9	18.8	70	Melphalan increased to 2 mg daily
April 6, 1979	9.7	21.6	84	Melphalan stopped (anemia)
June 1, 1979	10.7	16.9	66	No treatment
June 22, 1979	10.6	41.4	97	Melphalan restarted at 6 mg daily
July 2, 1979	8.8	12.8	90	Melphalan reduced to 4 mg daily
Aug. 10, 1979	10.2	25.0	89	Melphalan continued at 4 mg daily
Aug. 24, 1979	9.3	14.4	56	Melphalan stopped

Table 2
Vasopressin Stimulation and Water Deprivation Tests

	Urine Osmolarity	Serum Osmolarity
January 1977 Hospitalization		
Baseline	80	320
After vasopressin	580	320
June 1978 Hospitalization		
Baseline	90	320
After 16 hour water deprivation	170	360
After vasopressin	240	360

1978. A sixteen-hour water deprivation test was carried out followed by intramuscular administration of five units of vasopressin. The results are also shown in table 2. At that time her white blood cell count had risen to 94,600 with 20% polys, 31% bands, 11% metamyelocytes, 5% myelocytes, 13% lymphocytes and 19% monocytes. Splenic enlargement was now present on physical examination. No therapy for the leukemia was initiated. Desmopressin was substituted for lypressin with continued good control of the polyuria and polydipsia.

Because of the subsequent development of lethargy and malaise, chemotherapy with oral melphalan was started on June 22. She was treated with this drug intermittently as shown in table 1. Although the blood counts remained abnormal, treatment resulted in definite subjective improvement.

In March of 1979 the patient was admitted to the hospital for full mouth dental extraction for severely decayed teeth in association with a platelet count of 82,000. Simultaneous samples showed a serum osmolarity of 290 and a urine osmolarity of 130 after a twenty-four hour interruption of desmopressin therapy. A bone marrow carried out at this time showed 100% cellularity with 16% blasts and promyelocytes.

Subsequent to discharge the patient complained of progressively increasing malaise and lethargy, diffuse bone pain, and intermittent left upper quadrant pain with tenderness. The patient deteriorated rapidly and died in August 1979. No autopsy was performed.

Discussion

Diabetes insipidus is generally considered to be a rare disease, and its association with either primary or metastatic neoplasms is unusual. The tumor most frequently implicated in causing diabetes insipidus is metastatic breast cancer. In a review of thirty-nine patients with metastatic breast cancer and diabetes insipidus, it was found that in 27% diabetes insipidus was one of the initial manifestations that led to a diagnosis of recurrent disease.[4] However, the syndrome was always accompanied by the presence of other metastatic lesions, and the authors concluded that diabetes insipidus secondary to neurohypophyseal metastases occurred late in the course of the disease.

Although destruction of the posterior pituitary by metastases seems to be the mechanism producing diabetes insipidus in association with solid tumors, necrosis secondary to vascular occlusion can apparently cause diabetes insipidus in patients with leukemia.[2] Since no autopsy was obtained in the present patient, it is not possible to know if the diabetes insipidus was secondary to invasion by leukemic cells or to thrombosis from vascular occlusion. Factors against tumor involvement are the failure to develop additional hypothalamic or pituitary abnormalities during the initial eighteen months after diagnosis when she received no antileukemia therapy, the development of diabetes insipidus prior to evidence of additional organ infiltration such as splenomegaly or hepatomegaly, and the unchanging severity of the diabetes insipidus during the course of the leukemia, which included periods of both exacerbation and apparent control with chemotherapy. Although central nervous system dysfunction was apparent for several days immediately prior to the patient's death, infection, hemorrhage, or other factors could easily have been responsible for this. This is of some importance, since a course of cranial radiation therapy might be expected to benefit a patient with a leukemic cell mass, but would not be indicated if thrombosis were the cause.

Only two of the five adequately reported cases of chronic myelogenous leukemia in association with diabetes insipidus were autopsied, and both demonstrated leukemic infiltration of the pituitary.[2] In the only case reported in the English language literature, the leukemia was far advanced when the diabetes insipidus developed.[5] In other instances where diabetes insipidus has been found in association with leukemia, it has been noted that this is usually a late complication of the disease.[3] The patient reported in this paper is most unusual because of the rare association of diabetes insipidus with chronic myelogenous leukemia and because the diabetes insipidus was the earliest clinical manifestation, being present prior to the diagnosis of the leukemia.

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Solitary Thyroid Nodules in the Community Hospital: Use of the Percentage Cancer Index

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• *This paper presents the results of a five year study of solitary thyroid nodules and suggests an algorithm for managing patients with such nodules.*

MANAGEMENT of solitary thyroid nodules continues to present a problem for the practicing physician. Although it is obviously important to detect and surgically treat cancer of the thyroid, it is also important to minimize unnecessary operations. Recently we reported on the operations for solitary thyroid nodules carried out in our community hospital during the three year period 1979 through 1981.[1] Cancer was found in 10 of 153 patients, giving a 6.5 percentage cancer index (PCI). The PCI is the percentage of operated patients in whom cancer is found.

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Since then we have extended the survey for two additional years, 1982 and 1983, providing a total survey period of five years. Figure 1 shows the total thyroid and nodule operations performed, the PCI, and deaths due to thyroid cancer for each of the five years. From 1979 through 1982 the yearly thyroid and nodule operations ranged from 58 to 69 and 46 to 54, respectively. In 1983 there were unaccounted-for decreases to 39 and 29, respectively. Nevertheless the PCI fluctuated from 2 to 7.4 percent per year. The low PCI plus the fact that only 13 patients with thyroid cancer were found over five years in a community of over 250,000 persons supports current evidence that thyroid cancer is uncommon.

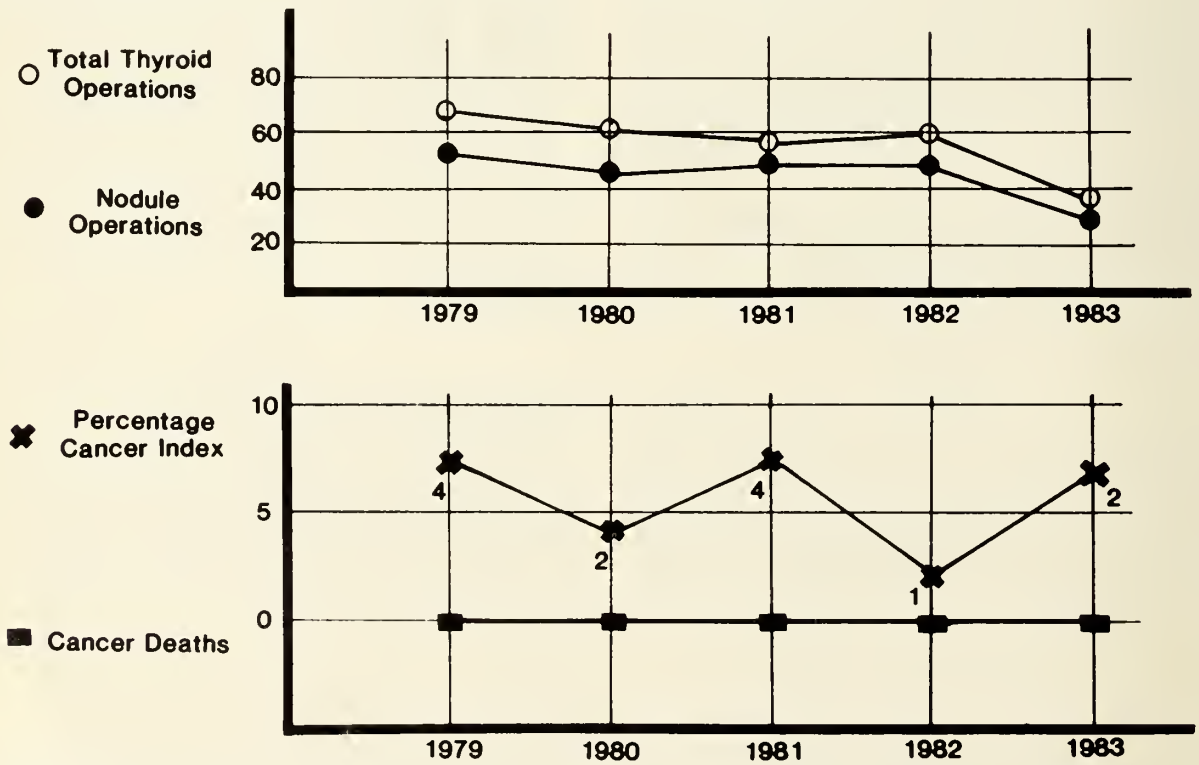


Figure 1. Total thyroid and nodule operations, percentage cancer index and cancer deaths for each year 1979 to 1983 at New Hanover Memorial Hospital. The numbers below the percentage cancer index line represent the actual numbers of cancer cases per year.

Table 1 shows demographic data for the 231 nodule operations. The largest number was performed in white women between the ages of 20 and 60. The prevalence of cancer according to sex, race and age is shown in table 2. The highest percentages of cancer were found in white women younger than 20 and in white men, suggesting that these groups have the highest risk. Table 3 shows the type and extent of cancer for the 13 patients. The overall PCI was 5.6%, 13 of 231 patients having cancer.

In our recently published report we reviewed the PCI in the medical literature over the last 38 years.[1] These data substantiate the usefulness of the PCI as a clinical index. It varies widely, depending on thoroughness of the preoperative evaluation. We separated the reports into three groups: In group 1, "all" patients with nodules went to surgery; in group 2, certain methods were employed to screen patients prior to surgery, e.g., clinical evaluation, radioactive iodine scan, sonogram and thyroid suppression; and in group 3, fine needle aspiration (FNA) was employed in addition to the screening methods in group 2. The PCI ranged considerably among the groups with the averages being 13.8%, 21.8% and 27.9%, respectively. Thus the PCI of 5.6% found in our survey would be considered low and indicates that many patients were operated on for the few patients found to have cancer.

Table 1
Demographic Data — Thyroid Nodule Operations, 1979-1983

	Ages				
	<20	20-40	40-60	>60	Total
Women					
White	9	65	63	19	156
Black	1	19	18	10	48
Men					
White	—	11	7	2	20
Black	—	2	3	2	7
Total	10	97	91	33	231

Table 2
Prevalence of Cancer in Thyroid Nodules, 1979-1983

	Ages			
	<20	20-40	40-60	>60
Women				
White	2/9 (22%)	3/65 (4.6%)	2/63 (3.2%)	—
Black	—	2/19 (10.5%)	—	1/10 (10%)
Men				
White	—	1/11 (9.1%)	1/7 (14.3%)	1/2 (50%)
Black	—	—	—	—

Table 3
Characteristics of Thyroid Cancer in 13 Patients, 1979-1983

Papillary Carcinoma — 11 Cases

2 patients — <1 cm
3 patients — 2 cm, 2 with capsular invasion
4 patients — 2 to 5 cm, 3 with invasion
2 patients — multifocal
2 patients with positive nodes

Follicular carcinoma — 2 patients
2 and 3 cm with invasion

How can the PCI be improved so that patients with cancer can be detected more accurately? The answer is multifactorial and requires a clear understanding of the many clinical and laboratory features involved. As shown in our survey, the highest risk groups are those persons less than 20 years of age, and white men. Various types of goiter are common in middle-aged white women, but this is the lowest cancer risk group. A history of definite recent growth and radiation therapy to the head and neck are well known high risk factors. A multinodular goiter or simply an enlargement of the contralateral lobe of the thyroid is usually a low risk finding for cancer. Serum measurements for thyrotropin to diagnose hypothyroidism and thyroid antibodies to diagnose Hashimoto's thyroditis are often helpful. Although papillary carcinoma can occur with Hashimoto's thyroiditis, this is a rare occurrence. Thyroxine for hypothyroidism and goiter suppression is the appropriate therapy for Hashimoto's thyroiditis. However if the nodule increases or a new nodule appears, cancer must be considered. The incidence of lymphoma, rarely associated with Hashimoto's thyroiditis as a large symptomatic nodule, may be increasing. It may be best diagnosed by needle biopsy prior to surgery, since radiation treatment may be indicated.[2] Triiodothyronine resin uptake values of serum should always be performed along with serum thyroxine levels to assess for an abnormality of thyroxine binding protein.

Perhaps the most confusing issue is that of a cold nodule found by isotopic scan. It must be emphasized that at least 85% of cold nodules are not cancer. Most are colloid nodules. A nodule showing decreased uptake (vs truly cold) is even less likely to be cancer. Actually the greatest use of a scan is to detect the functioning nodule, warm or hot, in which cancer is rarely found. Sonograms are helpful in delineating clinically suspicious cysts or mixed solid-cystic lesions.

If a trial of thyroid suppression is undertaken, an adequate dose of thyroxine, 0.2 to 0.3 mg daily, must be employed with regular follow-up exams. Preferably the thyrotropin level should be suppressed to less than 2.0 μU/ml and should not rise after thyrotropin stimulating hormone administration.

For the highest possible PCI at the lowest cost, FNA should be utilized.[3, 4] This technique has been slow to be employed in the community hospital setting because it has been stated that ten cases per week are needed to maintain adequate technical competence.[3] As more experience has accumulated, it has become apparent that aspiration can be performed by a properly trained physician whose experience is considerably more limited. The aspirate[5] or slide can be mailed for pathologic interpretation if sufficient expertise is not available locally. FNA of thyroid nodules has been considered by some investigators to have up to 95% accuracy with a 99% specificity and a 73% sensitivity.[3] A recent report, however, found false positive and false negative results of 24% and 9%, respectively.[6]

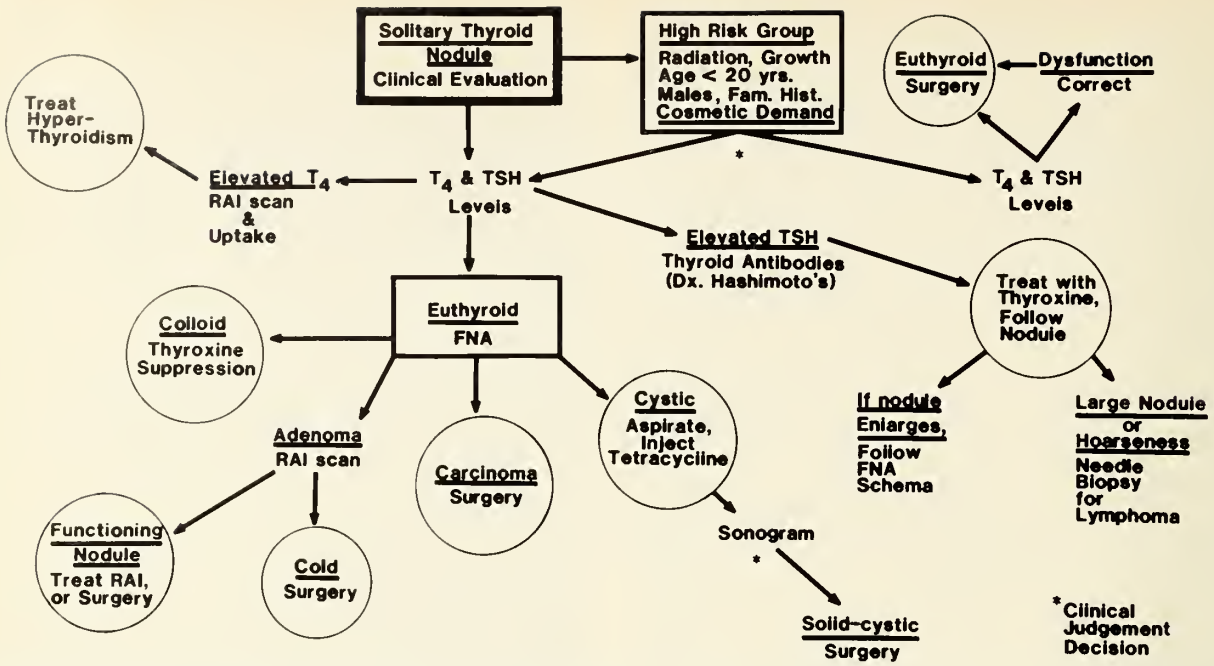


Figure 2. Algorithm for the management of solitary thyroid nodules in a community hospital setting. Abbreviations: FNA, fine needle aspiration; T_4, thyroxine; TSH, thyrotropin; RAI, radioactive iodine.

Utilizing FNA, the PCI of nodule operations should range from 50 to 78% in a standard clinical setting, even when some patients request nodule removal for cosmetic reasons or undue cancerphobia.

Based on the above considerations and the recommendations in the literature, we would currently suggest the algorithm outlined in figure 2 for managing thyroid nodules in a community hospital setting. This algorithm assigns FNA to a central role assuming that the appropriate expertise of aspiration, fixation and interpretation is available. The algorithm does not employ large needle aspiration, which is considered an important diagnostic step after FNA by some,[4] because considerable additional expertise is necessary.

Opposition to this algorithm might be raised because of a recently published decision analysis study which compared mortality and morbidity as end points for three treatment options for "cold" nodules. The options were 1) immediate surgery, 2) thyroxine suppression to select malignant nodules, and 3) FNA to determine the necessity of surgery.[7] Interestingly a significant difference was not found among the three options. Although this appears to be important information, it does not take into account several other clinical considerations such as the initial laboratory and radiologic studies needed for assessment of the solitary nodule, the time needed to make the diagnosis, patient acceptance, and cost. Nevertheless this analysis does indicate that if FNA is not available in a community, a radioactive iodine scan and sonogram could be substituted without affecting patient morbidity and mortality. Cold solid nodules could be managed by either immediate surgery or thyroxine suppression with surgery for nodules that do not regress. Patients with cytological results by FNA that were indeterminate or suspicious could be managed by either option. No matter which approach is employed, we believe that periodic review of the PCI should be helpful in following the success of local management. Finally, we must caution that no single algorithm will take into account all the clinical variables possible.[8] Clinical judgment is essential.

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North Carolina Medical Journal

Features for Patients October 1984

Some Useful Things to Know About the Heart

Norman J. Robinson, M.D.

Chest Pain

Chest poin causes concern since it is o common symptom of cardiovasculor disease. There ore o number of possible couses of chest poin, however, some serious ond some not, which mokes this o perplexing symptom for potients ond physicions olike.

Cordiovosculor disease is the leoding couse of deoth in the Western world, cousing opproximotely twice as many deoths os concer. Coronory heort diseose, which results from foty deposits blocking the coronory orteries, is responsible for ninety percent of the deoths due to heart diseose. Congenitol heort diseose, cardioc complications of high blood pressure, ond rheumotic heort diseose make up the other ten percent of cordioc deoths.

Coronory heort diseose usually first monifests itself in one of three woys: ongino pectoris, heort ottack, or sudden death. **Angina pectoris** is the nome given to recurrent chest poin or chest discomfort, usually during periods of activity. It is brought obout by impoired oxygen supply to the heort muscle. This pain is usuolly experienced os a pressing or squeezing discomfort beneoth the breost bone, ond moy be occomponied by a feeling of similor discomfort in the neck, jaw, arms or shoulders. It moy take other forms, however, such os oching, pressure or choking, ond sometimes o feeling of numbness in the arms ond hands.

Heart attack is synonymous with **myocardial infarction,** ond implies destruction of o portion of the heart muscle due to complete obstruction of one or more of the coronory orteries. A heort ottock is usuolly occomponied by chest pain, somewhot similor to that of ongino pectoris, but usuolly more severe. It is not usuolly reloted to activity, ond frequently it is occomponied by other symptoms such os shortness of breath, sweating and nausea.

Sudden death moy be the first monifestation of coronory heort disease, but it is often preceded by subtle symptoms which, if heeded, might lead to preventive oction. Heort ottock ond sudden deoth ore frequently herolded by new onset of ongina pectoris, by worsening ongino pectoris, or by development of onginal pain during non-stressful periods, such os during rest or sleep.

A sometimes confusing factor is thot poin which is similor in locotion and which hos the some chorocteristics as coronory heort diseose con orise from other sources such os the esophogus, stomoch, goll blodder, lungs, spine ond chest wall. In oddition, other types of cordiovasculor problems moy cause similor symptoms.

The circumstances in which the pain occurs may provide clues as to its source, such os whether it is brought on by physicol effort, meols, swallowing, different types of movement, breothing, or lying in o particulor position. Frequently there ore many disorders thot ore capoble of cousing o potient's pain pottern. Often the cause can be found only by coreful evoluotion ond considerotion of all of the possibilities.

Since chest pain moy orise from several sources, some potentiolly serious and some not, one should seek prompt medicol attention when this symptom develops. Since fifty percent of deaths from heort ottocks occur within two hours of the onset of symptoms, the importonce of promptness cannot be overemphosized. Many of these deaths con be prevented if prompt medicol attention is sought. Therefore, one should not ignore chest poin or woit for it to go owoy, but should seek evaluotion in o physicion's office or emergency room.

When evaluoting chest pain, the physician will first attempt to define the noture of the poin by asking obout its locotion, intensity, durotion, the situotion in which it developed, and other detoils about its chorocteristics. Evoluation will usuolly include a physical exominotion ond on electrocordiogrom. Additionol loborotory and possibly x-ray tests moy be required depending upon which sources of poin seem most likely ofter

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the initiol exomination.

More often than not, it will be determined thot the potient's chest pain is not reloted to o cordioc problem, but is from o benign source which can be eosily treoted. On the other hond, if the poin is found to be due to heort disease, prompt attention moy be life-saving.

If o patentiolly serious heart problem is suspected, precoutions moy be token such os admitting the potient to the hospital ond placing him/her on o heort monitor to determine if the chest poin is due to o heort ottack or impending heort ottack. This determinotion may require severol days, and if the source of pain remoins uncertoin, odditionol testing may be required.

The electrocordiogrom is a very important test which helps the physicion decide on the likelihood of chest poin being due to heort diseose. Since there are many variations of normol, comporison with o previous electrocordiogrom on the some person provides voluoble informotion. For this reoson, it is wise to be sure of the avoilobility of ony old electrocordiogroms for future comporison. A person who onticipates moving or traveling a great deol should corry o copy of o previous electrocordiogrom.

Becouse of the complexities ond potentially serious implicotions of chest poin, one should nat feel reluctont or embarrossed obout seeking prompt ottention. A "prepore for the worst ond hope for the best" opproach is preferred since it moy be life-soving os well os comforting.

CPR

Approximotely 1.5 million Americons suffer heart ottocks onnuolly and obout 40 percent of them die. Over holf of the deoths take ploce outside of o hospitol and occur within two hours ofter the onset of symptoms. These deoths ore due to sudden cardioc orrest, usually resulting from severe irregularity of the heart. Thus, sudden deoth from coronary heart diseose is our most important medical emergency.

Successful resuscitotian is the only chonce for survivol for a substontiol number of these patients whose deoths can be prevented by prompt, appropriate treatment and early entry into the emergency medical system. Victims of drawning, electrocutian, suffocatian, drug intoxicotion, and automobile occidents can often be soved by the same type of prompt resuscitatian.

It hos been almost twenty-five yeors since externol chest compressian wos introduced, offering some hope far decreosing the more thon 1000 sudden deoths thot occur doily in the United States. In 1966, cordiopulmonory resuscitotion (CPR) troining was recommended for medicol personnel, using standards estoblished by the American Heart Assaciotion. In 1973, o National Conference on Stondords for Cordiopulmonory Resuscitation and Emergency Cardiac Core, sponsored by the Americon Heart Association ond the Nationol Academy of Sciences/ Notianal Reseorch Council, recommended thot

1. cardiopulmonary resuscitation troining be extended to the generol public;
2. training be in accordance with the standords af the Americon Heort Associotion;
3. certificatian for competency be based an notionally stondordized curriculo.

The Americon Red Cross, American Heart Assaciation ond other agencies were defined as providers of this training.

Since 1973, odditional conferences, the lotest by the Americon Heort Associatian in 1979, have modified the guidelines for troining in CPR. Through these conferences, specific stondords have been adopted for troining and certification in basic life support (BLS) and odvanced cardiac life support (ACLS). BLS training, in addition to teaching CPR through closed chest massage and artificial respiration, has been broodened to include recognitian of symptoms af a heort attack, control of cordioc risk foctors, manogement of victims of oirwoy abstruction, ond use of emergency medicol services. This troining is ovoiloble to all loy people ond is required of emergency medicol personnel and most hospital personnel. ACLS involves the use of intravenous fluids, medicotions, mechonical ventilotion, ond electric heort shock, ond is given as specialized troining far poromedicol ond medical personnel.

Since troining in CPR become availoble to large numbers of loy persons, along with development of ropid tronsport systems monoged by well-trained poromedicol personnel, survivol from sudden death has improved substontiolly. Without prompt CPR by bystonders, however, successful resuscitotion is less thon holf as likely despite the availability of a well-trained poromedicol ombulance team. Thus, the role of the lay bystander is indispensible to successful resuscitotion of the cordioc orrest victim.

It has been estimoted thot o well-troined lay public, along with o well-developed emergency cordioc care system, may save between 100,000 and 200,000 lives onnuolly in the United States. As many os 43 percent con survive cordioc arrest due to heart rhythm disturbances if BLS is begun by troined persons within four minutes of the orrest ond o transport teom trained in ACLS orrives within eight minutes of the orrest. This mokes it cleor thot the community ot large is the "ultimate coronory core unit."

Whereas BLS troining is valuoble for onyone, it moy be of particular impartonce ta individuals who work with lorge groups of people or who live or work with people who have or are predisposed to cordiovasculor disease. Troining ond certificotion in BLS moy be orranged through locol American Red Cross and Americon Heort Association chapters. These programs use standardized training and testing methods. Persons interested in maintaining certification

must be retested annually.

The "model" system of complete emergency cordioc core must include basic life support, advanced cardiac life support ond on efficient tronsport service. Basic life support is the holding oction which will mointoin effective circulation and respiration for o limited period of time until odvonced cordioc life support ond tronsportation ore ovoiloble. In communities with large numbers of lay persons troined in BLS ond with o ropid response system of troined ACLS personnel, lorge numbers of sudden deoth victims hove been saved.

Palpitations

The word **palpitation** is derived from the lotin word **palpitare** which meons "to throb." It is used to describe on aworeness of heort oction such os feeling of the heort beoting irregulorly or faster or more forcefully thon usuol.

Awareness of the heort beot commonly occurs when the heart rote increoses in response to normol stimuli such os exercise, excitement, or fright. In addition, mony people occosionolly experience o feeling of skipping or "flip-flopping" of the heort due to premature beots. When these occur occosionolly in o heolthy individuol who is free of other symptoms, they are generolly felt to be benign.

In controst, palpitotions that ore not provoked by onxiety, thot occur frequently, or thot ore associoted with other symptoms such os chest poin, shortness of breoth, dizziness, or spells of possing out, moy indicote significont disturbonces of heart rhythm which require evoluotion and theropy. Such disturbonces moy be due to heort diseose or may be secondory to some other illness such os onemio, excessive thyroid function, or infection. Additionolly, such disturbonces moy be due to excessive stimulotion of the heort by such things os coffee, teo, tobocco, or drugs. Emotionol disturbonces moy also be responsible for excessive owareness of heort oction.

Persons experiencing palpitotions should toke coreful note of the circumstonces in which they occur ond, in porticulor, ony relotionship to time of day, excitement, stress, physicol octivity, and stimulant beverages. Additionolly, coreful note should be token of other ossociated symptoms. This kind of information is voluable to the physicion's understonding of the symptom.

Persons who consult their physicion becouse of polpitotions usually require coreful questioning as well os a physical examinotion. An electrocardiogrom ond other loborotory tests are usually included in the evoluotion. If these do not provide sufficient information, odditionol testing, such os o treodmill stress test ond a 24-hour tope recording of the patient's electrocardiogrom while he is engoging in normol activities, may be considered. The purpose of the evaluation is to confirm the presence of o heort rhythm disturbonce, to determine its type, ond to detect ony association with heort diseose or other illness.

Once the cause of polpitations is understood, judgment can be mode os to the implications ond need for theropy. Generolly, physicians will toilor the aggressiveness of their evaluotion ond therapy to the severity of the potient's symptoms and the seriousness of any underlying illness. Theropy may ronge from reassuronce to intensive medical theropy. In all instonces, therapy is intended to reduce symptoms, to olleviate or control underlying conditions, or to prevent development of more serious problems.

Hair Today, Gone Tomorrow — Alopecia

Russell W. Eyre, M.D., Claude S. Burton, M.D. and J. Lamar Callaway, M.D.

Boldness hos been considered o curse since eorly recorded history. Isoioh, in the Old Testoment, worned thot oll the hair would be removed from the doughters of Zion becouse of their wickedness. Julius Caesor tried to camoufloge his bolding scolp by combing his hoir forword. A full heod of hoir has been considered o mork of youth and beouty.

All mammols hove hoir. Most hove a thick coot over their entire body to protect them from the elements. Mon hos most of his body covered with fine lonugo hairs. Long terminol hoirs ore present on the scolp. The only spots normolly hoirless are the polms ond soles. In the developing fetus hair begins to grow early, within the first three to four months after conception. This fine lonugo hair is shed about one month before birth. The second coot of hair is then shed within the first yeor of life. Cycles of

shedding and growth cantinue thraughaut aur lives, but the cycles are nat caardinated after the first few.

Each hair has a grawth phase called anagen. The length af this growth phase determines how lang a hair will graw. Hair graws abaut ane inch every twa months. Ta graw a hair ane faot lang wauld take an anagen phase af twa years. Most anagen phases last abaut three years. The resting phase af a hair is called telogen. This phase usually lasts three manths. The transitian between a growing and resting hair is called catagen.

Nine aut af every ten hairs are in anagen phase. A hair is shed when a fallicle halding a resting hair begins ta farm a new hair. This new anagen hair pushes the telagen hair aut of the fallicle. Abaut one hundred hairs are shed this way every day. Hairs are dead once they emerge fram the fallicle. The anly living partion af a hair is buried deep in the skin. The narmal density af hair is ane thousand hairs per square inch. Half of the hoirs in one oreo may be lost before it becames noticeably thin. The normal scalp hos abaut one hundred thousand hairs ond this moy weigh fram faur to ten ounces, depending on the length.

There are many types of hair lass. Two general categaries are those thot produce scarring in the hoir follicle ond those that don't domage the follicle. Alapecia or baldness that is coused by scarring is aften produced by an infection of the hoir follicle but may olso be caused by burns, radiotion ar skin cancers. There are na follicles left to regrow hair in those areas. However, non-scarring olopecias merely have long terminol hoirs replaced by short fine lanugo hairs. Occasionally these fine lanugo hoirs may begin to produce long terminal hairs agoin. The non-scorring alopecios can be subdivided into those producing localized ond those praducing generolized hair loss. Generalized hoir loss is usually caused by o toxic effect on the hoir roat. Severe illness with high fevers, vitamin deficiencies, endocrine diseases, pregnancy, cancer chematherapy and variaus paisons may all cause this toxic diffuse alapecia. Nan-scarring localized alapecia is usually either alopecia areata ar male pattern baldness.

Alapecia areata usually accurs in patients yaunger than twenty-five. Patches af scalp hair fall aut almast overnight. The beard, eyebrows, eyelashes, and pubic hair may alsa be affected. The grawing cycle is abruptly stapped and many anagen hairs change ta telagen hairs. These hairs are weak and break aff easily. The raat af the hair is surrounded by cells that usually fight infectian. These cells appear ta put the fallicle ta sleep. The cause af alapecia areata is unknawn, but many patients regraw their hair within several manths or years.

Male pattern ar camman baldness affects eighty percent af all males by eighty years af age. In ane aut of twenty males same farm af camman baldness is seen before age twenty. It is so frequently seen thot it should be considered o normal part of aging. Hair loss occurs in distinct patterns, beginning with frontol recession ond progressing to loss over the entire top of the head leaving only o smoll ring of narmol hairs at the lower portion of the scolp. The follicles in the bold orea have stapped producing terminal hoirs. Only fine soft short lonugo hoirs are present.

Occosionally women with tumors that produce male hormones hove male baldness. Eunuchs — men who were castroted before puberty — never develop male pottern baldness. It is obvious that this "normol" feature of aging, common baldness, is hormonally reloted. However the precise mechanism of this hormonol oction is unknown. Genetics and age olso play a role. Baldness is rore in same races, especially in the Indian and Oriental races. Local foctors such os hoir style, frequency of hoir cuts, ond the weoring of hots do not influence the course af male pattern olopecia.

The cause af the alapecia must be determined befare treatment is started. If the alapecia is nan-scarring there is a passibility af hair regrowth when the cause is remaved. Taxins, severe illness or endacrine imbalances are usually evident fram ather symptams. Alapecia areata may respond ta treatments that affect a lacalized immune respanse such as steraids, light treatments, irritants, ar allergens. Almast every cream ever farmulated has been tauted by someone to help regraw male pattern hair lass. Until recently all those claims have been unfounded.

Ten years aga a powerful new drug used ta treat high blaad pressure was naticed ta change fine, soft lanuga hairs to darker, langer, terminal hairs. This change was very disturbing especially when it occurred an the face of yaung children. When this drug, Minaxidil, was put inta a latian it restored the frantal hair loss seen in same apes. Clinical trials in humans are currently in pragress. Mony questions remain unanswered obout the topical use of this medicotion, and the Federol Drug Enforcement Agency hos not approved its topicol use. The dermatologic clinicol triols unit ot Duke University Medicol Center is participating with o number of other medicol centers in studies directed ot answering those remoining questions.

When skin containing long terminal hoirs is tronsplanted to areos containing lanugo hairs the terminol hairs da not chonge their oppearonce. In male pattern baldness, the technique of tronsplanting hoir from the ring of normol hair olang the lower scolp to the top of the scolp hos grown into o multimillion dollor business. Excising a partian of bold scalp may be combined with hoir tronsplonts to produce a satisfactory result. However the procedure is expensive, painful, and not without hozards.

The judicious use of o wig or hoir piece con be the eosiest ond leost expensive approoch to solving the curse of olopecio.

You Better Look Behind the Ears

Jorge J. Gonzalez, M.D.

• *Mysterious loss of thirty pounds by an elderly woman is explained by looking behind her ears.*

NOT long ago, a 71-year-old woman was referred to our university clinic for the evaluation of severe weight loss (30 lb) over the preceding three months. She had had a left middle ear infection three months previously, associated with vertigo and some nausea. She was treated with antibiotics, and a myringotomy tube was placed. After this episode, her appetite decreased markedly, and she lost her taste for food. She felt that after chewing food for a few seconds, the food grew into a "big tasteless wad," and she could not swallow it. An attempt to elucidate the cause of her weight loss resulted in an extensive radiological and biochemical evaluation which was negative.

Her review of systems was noncontributory. Her past medical history was remarkable only for mild hypertension for which she was taking a thiazide diuretic. She denied the use of any other medications.

Physical examination revealed an emaciated female in no acute distress. The only positive findings were the presence of a transdermal scopolamine patch (Transderm V) in the left retro-auricular area and an extremely dry buccal mucosa. On questioning, the patient stated that she had been using the patches every three days. They had been prescribed for the relief of vertigo and nausea, and they had been extremely successful in doing this. After stopping using the patches, the patient developed a voracious appetite, and rapid weight gain ensued.

The inhibition of salivary secretions by antimuscarinics is well known. In this case the chronic use of low dose scopolamine via transdermal absorption apparently produced marked weight loss by interfering with salivary secretion. It is remarkable that no other antimuscarinic side effects were evident.

In these days of improved drug delivery systems, one needs to carefully explore every inch of skin before embarking on an extensive workup. Possibly induction of Sjogren's syndrome with transdermal scopolamine is warranted in some cases of morbid obesity.

From the Department of Medicine, New Hanover Memorial Hospital, Wilmington 28401.

The History That Wasn't

Norman J. Robinson, M.D.

• *A middle-aged man with a "heart condition" is restored to complete health, and the value of history taking is underscored again.*

IT all seemed pretty straightforward. The fifty-year-old moderately rotund man had recently moved to our quiet beach community after escaping from the hectic life of a business executive. To occupy himself and keep food on the table, he had purchased a small motel.

He came, complete with bottles of Isordil and nitroglycerine, to find a new doctor for his "heart condition." He told of having been hospitalized several months previously with an episode of severe chest pain. Since then, he had had repeated milder episodes of pain, always relieved promptly by nitroglycerine. He felt that he was doing reasonably well and wished to keep medical expenses to a minimum since he had not yet replaced his medical insurance and knew that his condition would bring with it a fearful policy premium. He did consent to an electrocardiogram which revealed nonspecific ST-T changes.

After several months of doing well, he returned in the midst of the tourist season to report worsening chest pain. "I can hardly do anything without getting chest pain," he said. "Why, I can't even make it across my motel parking lot without stopping to take a nitroglycerine tablet." (Still no medical insurance.) Sounds pretty bad, I thought. After some debate over how best to approach the problem he consented to taking more medicine — bigger Isordil tablets and a beta blocker.

Within several days, his symptoms were much better and the motel business was thriving. A couple of months later, however, he presented again with worsening chest pain. "Why, I can't even walk across my motel parking lot without having to stop to take a nitroglycerine tablet." (Still no medical insurance.) Things are getting worse, I thought. After some discussion, he consented to more medication — nitrates plus a bigger beta blocker. Within a few days, his symptoms were much improved.

Several months later, my patient returned to report a strange and marvelous occurrence. He had made a trip to London to attend a friend's funeral. On the airplane crossing the Atlantic Ocean, he was suddenly seized by crushing chest pain and discovered, to his horror, he had left his nitroglycerine tablets at home. The stewardess, wishing to avert a calamity and having little else to offer, gave him a hefty dose of Maalox. Miraculous, immediate and complete relief of his pain ensued. "Now I get quicker relief with Maalox than with nitroglycerine, even when I walk across my motel parking lot," he exclaimed. I quickly came to the obvious conclusion: "something's not quite right." He consented to some tests. On the treadmill, he had the endurance of an Olympic athlete and had no chest pain or ischemic changes. His upper GI series revealed a substantial hiatal hernia, gastroesophageal reflux and esophageal spasm. An antireflux regimen eliminated all of his symptoms and his cardiac medicines were stopped.

Still bewildered by the entire situation, I felt compelled to resort to a basic technique: history taking. "Tell me more about walking across the motel parking lot. What does that involve?" "Well," he said, "I frequently walk across the parking lot to check the rooms. Since my guests dump trash out of their cars onto my parking lot, I usually bend over to pick up trash as I go. Come to think of it, that's when I get the chest pain."

From the Department of Medicine, New Hanover Memorial Hospital, Wilmington 28401.

"Tips" on Acute Arthritis and Clubbing

Nancy B. Allen, M.D.

• *Two color photos beautifully illustrate the painful effects of hypertrophic osteoarthropathy in a patient whose endometrial cancer had metastasized to a lung.*

As physicians, we must always pay attention to the patient. New symptoms or signs usually mean something. This is especially true in a patient with cancer, as you will see in this report.

A 50-year-old woman was hospitalized with fever, cough, joint pains and painful enlargement of her fingertips and toes. She had been well until 22 months previously when she underwent hysterectomy for excessive bleeding. A small and apparently incidental endometrial carcinoma, not involving the myometrium, was discovered; no further therapy was deemed necessary. Sixteen months after surgery she began complaining of pain in the region of the coccyx, eventually with weight loss and constipation. Rectal examination revealed a 2 cm mass along the left pelvic sidewall. A second operation was performed and this mass was found to be metastatic adenosquamous carcinoma, with all nodes negative. Postoperative local radiation with 4500 Rads was administered.

One to two weeks before admission, she noted gradual worsening of fever, dry cough, further weight loss, anorexia, and pain of the wrists, small hand joints, knees, ankles and toes. On admission, her temperature was 38.5° and there was prominent clubbing of fingers and toes, symmetrical polyarthritis involving distal joints (figure 1), and tenderness along both distal tibias. Lung examination was normal.

Laboratory results were nonspecific, with hematocrit 34%, normal white blood count, platelet count 611,000. Chest x-ray (figure 2) showed a solitary, 1.5 cm pulmonary nodule in the right lower lobe. Thin needle aspirate of this nodule showed adenosquamous carcinoma. Radiographs

From the Department of Medicine, Duke University Medical Center, Durham 27710.



Figure 1. *Fingers, toes and right ankle showing joint swelling and clubbing.*



Figure 2. *Chest radiograph with peripheral 1.5 cm right pulmonary nodule overlying rib.*

of the hands and feet (figures 3 and 4) showed typical changes of hypertrophic osteoarthropathy.

The patient's pain and fever did not respond to antibiotics, fluids, and acetaminophen. We saw her and suggested treatment with ibuprofen 600 mg QID. Within 24 hours her temperature decreased and her joint symptoms improved markedly. Direct cancer therapy with cis-Platinum and radiation to the lung and mediastinum led to continued improvement in the clubbing and arthritis, even when ibuprofen was stopped. However, she died of progressive metastatic cancer six months later.

Discussion

This patient developed clubbing and arthritis simultaneously with the discovery that her endometrial carcinoma had metastasized to the lung. Hypertrophic osteoarthropathy (HOA), or hypertrophic pulmonary osteoarthropathy as this syndrome was called previously, occurs in the setting of a variety of pulmonary and extrapulmonary conditions. The former include primary or metastatic neoplasms, infections (empyema, bronchiectasis, lung abscess, tuberculosis), cystic fibrosis, and bronchogenic cysts. Extrapulmonary conditions associated with the development of HOA include bacterial endocarditis, gastrointestinal infections, cirrhosis, inflammatory bowel disease, endocrine disorders, and neoplasms (gastrointestinal, renal, lymphoma, chronic myelogenous leukemia).

The classic triad of hypertrophic osteoarthropathy is arthritis, periostitis and clubbing. The arthritis generally involves the wrists, hands, knees, ankles, and feet and may mimic rheumatoid arthritis. It is often very painful and accompanied by fever as in our patient. The periostitis causes distal long bone pain of varying severity, which is increased by dependency and relieved by elevation. The description of clubbing dates back to Hippocrates in 400 B.C. who described softening and accentuated convexity of the nail and loss of the normal 15° angle between nail and nailbed. Local warmth, swelling and erythema may be seen as in the photographs of our patient. Physical examination



Figure 3. *Proximal phalanx of finger showing fluffy periostitis.*



Figure 4. *Distal lower extremities with prominent soft tissue swelling and periostitis.*

reveals symmetrical clubbing in fingers and toes. Edema occurs in the hands and feet; warmth, tenderness and less often redness are noted over the feet, legs, and forearms. The skin may appear shiny. Symptomatic joints often show effusions and limited motion.

Epidemiologically, HOA affects men and women equally. Age distribution reflects that of the underlying disorder. The erythrocyte sedimentation rate may be elevated, but no specific tests are available for diagnosis. Synovial fluid is generally non-inflammatory.

Radiographic findings consist of periosteal thickening along the long and short bones. Initially there is a thin, continuous, sclerotic line separated from the bony cortex by a narrow lucent line; later, this periosteal new bone formation thickens and fuses with the cortex. Osteoporosis may appear in later stages. These changes are seen in the tibia, fibula, radius, ulna and later in hands and feet along phalanges. Bone scan demonstrates characteristic linear uptake along these bones and around affected joints.

Etiology of HOA remains speculative. Vagal stimulation, hypervascularity as a response to ischemia, local circulatory abnormalities, hormonal changes (elevated growth hormone, estrogen), tumor immune complexes, and prostaglandins have all been suggested to play a role. It is intriguing that the onset of our patient's HOA coincided with the development of pulmonary metastases from her endometrial adenosquamous cancer.

The most effective treatment of HOA is to treat the underlying condition. If that is tumor, as in the case presented here, surgical, chemotherapeutic or radiation therapy should be employed without delay. Anti-inflammatory drugs such as aspirin, ibuprofen, indomethacin, or corticosteroids, are often effective in reducing symptoms related to HOA. The course varies greatly, but dramatic relief has been described in the recovery room following removal of a primary lung cancer. Certainly our patient responded within 24 hours of beginning ibuprofen.

HOA is a triad of arthritis, periostitis and clubbing and in its typical form should alert the physician to search for an underlying or primary condition. Our patient's HOA acted as a marker for recurrent endometrial cancer, and was temporally related to pulmonary metastases and not to her primary or locally recurrent disease. Treatment with ibuprofen and subsequently with chemotherapy and radiation therapy substantially reduced her joint symptoms.

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Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGDT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation, see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

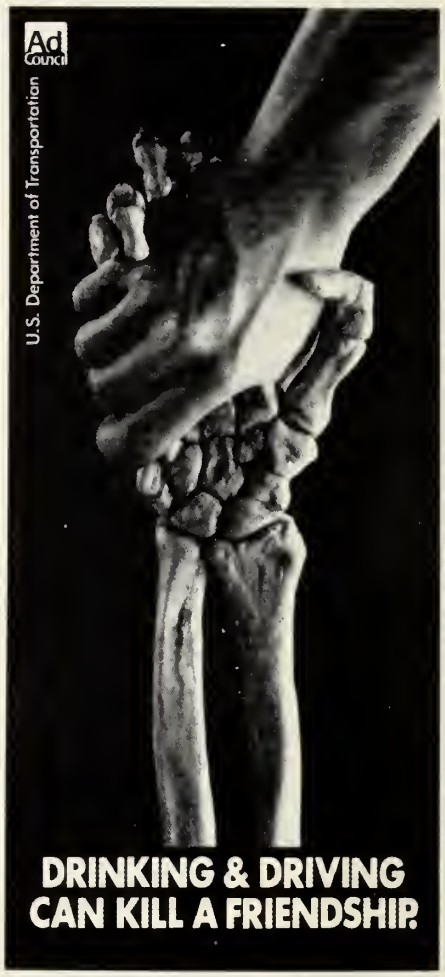
Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription. MED B-7-S

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Practice Patterns of Graduates of a North Carolina Community Hospital Internal Medicine Training Program

Peter C. Ungaro, M.D. and Jorge J. Gonzalez, M.D.

• *One answer to the question, Are AHEC's aims being accomplished?*

THE Area Health Education Center (AHEC) program of the University of North Carolina established primary care residency training positions in various community hospitals in the state. One of the objectives was to expose residents and students to high quality community hospital experiences. It was thought that a satisfactory experience in an institution remote from the university center would induce trainees to settle in areas of the state that had inadequate numbers of physicians. At the same time the presence of the training programs would stimulate continuing medical education and improve the quality of care in community hospitals, increasing their attractiveness to prospective practitioners.

The internal medicine training program at New Hanover Memorial Hospital in Wilmington was initiated in 1972. The hospital is a community institution serving the southeastern coastal area, currently with 468 operational beds. Five medical school graduates began residencies at the first year level in 1973. The first trainees to complete the full three years of postgraduate training required for board eligibility graduated in 1976. This report describes the locations and types of practices that the program graduates have selected.

In the last several years information has been published describing the career choices of graduates of internal medicine training programs.[1, 2] This report in part concerns itself with the contrast between graduates of the training program at New Hanover Memorial Hospital and the national experience.

Resident Data

In the seven-year period from 1976 through 1982 twenty-three residents completed a full three years of training in internal medicine at New Hanover Memorial Hospital. Of these, fifteen went into practice in North Carolina. Seventeen were graduates of American medical schools and six were graduates of foreign medical schools. One of the foreign graduates was an American citizen. Table 1 compares numbers of American and foreign graduates who entered practice in North Carolina. The foreign graduates were more likely to remain in the state. Table 1 also contrasts those who graduated from out-of-state American medical schools with those who graduated from North Carolina schools. All six of the North Carolina graduates went into practice in North Carolina, while only four of the eleven out-of-state graduates entered practice in this state. For the out-of-state American graduates, proximity to North Carolina had some impact. Adjacent states were considered to be South Carolina, Kentucky, Tennessee, Virginia, and West Virginia. Graduates of medical schools in these states were more likely to remain in North Carolina or the adjoining states as shown in table 2.

Practice patterns within the state demonstrate less clear differences as shown in tables 3 and 4. Foreign medical graduates were the most prone to practice near Wilmington. The seven graduates electing to practice in North Carolina towns of less than 30,000 were fairly evenly divided when compared on the basis of where they went to medical school.

Table 1
American vs. Foreign Graduates in NC Practice

Medical School	No. of Graduates		N.C. Practice	
American		17		10
North Carolina	6		6	
Other State	11		4	
Foreign		6		5
Total		23		15 (65%)

Table 2
Practice Site: North Carolina, Adjacent State, or Distant State

Medical School	No. of Graduates	Practice Site: North Carolina	Adjacent	Distant
Adjacent State	5	3	2	0
Distant State	6	1	2	3

From the Department of Medicine, New Hanover Memorial Hospital, Wilmington 28401.

Table 3
Practice within 75 Miles of Wilmington

Medical School	No. of Graduates	Local Practice
North Carolina	6	2
Other States	11	3
Foreign	6	4
Total	23	9

Table 4
North Carolina Practices in Smaller Towns (<30,000 Pop.)

Medical School	No. of Graduates	Smaller Towns
North Carolina	6	3
Other States	4	2
Foreign	5	2
Total	15	7

Only four of the graduates went on to subspecialty training as shown in table 5. Two did fellowships in cardiology, one in endocrinology, and one in gastroenterology. Three of these remain in North Carolina. One of the three is currently in training, but plans to enter practice in North Carolina.

Eight of the fifteen graduates who went into practice in North Carolina went into solo situations. Three joined group practices (table 6). The other four currently have academic, emergency room, outpatient clinic or fellowship positions. Five of the fifteen have practices in nearby counties. Four others have established careers in this county. Three participate in our teaching program as clinical faculty and one is a full-time faculty member who joined our unit in 1978.

Between 1976 and 1982, twenty-one additional residents had one or two years of training. One of the first year residency positions is reserved for residents going into fields other than internal medicine and seven graduates followed this route. Four terminated postgraduate training after one year, going into careers in the military, National Health Service, a nearby emergency room, and a local primary care practice. Two left after one year when their contracts were not renewed. They completed their internal medicine residencies elsewhere. Three transferred to our program to complete their training after an initial year in another institution. One of the three is currently completing a hematology-oncology fellowship. Finally, one resident entered a rheumatology training program after two years, following the now defunct "short pathway." Of the twenty-one residents who completed less than three years of training at New Hanover Memorial Hospital, four are still in training programs, while nine have established practices here in North Carolina. Contact with these graduates has not been as close as that with those completing three full years here.

Table 5
Primary Care vs Subspecialty Practice

Medical School	No. of Graduates	Primary Care	Sub-specialty
American	17	15	2
Foreign	6	4	2
Total	23	19	4

Table 6
Type of Practice in North Carolina

Medical School	Solo	Group	Other
North Carolina	3	1	2
Other States	3	1	0
Foreign	2	1	2

Discussion

The major objectives of the North Carolina AHEC program have been to increase the number and to improve the distribution of primary health care providers in North Carolina. Available evidence suggests that the decision to enter primary care internal medicine is related more to personal variables than to the type of medical school or residency program attended.[1] The values of the physicians planning academic and subspecialty careers are apparently different from those of physicians seeking primary care opportunities. A training program's greatest impact seems to be on practice location, and our data substantiate this impression. All North Carolina medical school graduates training in our program remained in North Carolina, and about one-third of the trainees who graduated from out-of-state American medical schools have also remained in North Carolina. It is likely that if our program had not been here, and our residents had found training positions in other states, then many would have entered practice in those states. Our foreign medical school graduates were especially prone to settle here. We might speculate that few of them would have been drawn away by family ties or other personal obligations, and the convenience of establishing a practice close to their training site was not outweighed by other considerations. In addition, it is gratifying to see that of physicians who established practices in North Carolina, nearly fifty percent did so in towns with populations of less than 30,000. It seems clear that our program has increased the number and improved the distribution of physicians in the state and our local area.

Further evaluation of the data on out-of-state graduates suggests that the distance of the medical school from North Carolina has an impact on the probability of remaining in the state. Graduates of closer schools are more likely to remain here or in adjacent states while those from distant states are more likely to settle at considerable distance from our training program, frequently in the state of the resident's medical school. Examples include an Indiana University graduate who is now in practice in Indiana and a University of Minnesota graduate who is now in practice in Minnesota.

The graduates of the program who have settled in the

Wilmington area have kept in close contact with the local faculty. We have had the opportunity to observe their professional growth over the years, and this has provided a gratification that is not uniformly available to medical school faculty. Some were first met when they rotated here as students, and we have watched as they have matured into effective and respected members of our medical community.

It would be inappropriate for us to take credit for the large number of our residents going into primary care internal medicine. However, our pattern is different from that of many other institutions. Current data suggest that over half of internal medicine training program graduates go on to subspecialize,[3] whereas only twenty percent of our graduates made this choice. This is not because of constricted opportunity. Every graduate who has desired subspecialty training has been placed. Several have become fellows at prestigious institutions, and we have heard considerable praise about them from the faculty with whom they have subsequently had contact.

It is of interest that our typical graduate elects to go into solo practice. Possibly this reflects the fact that solo practice is a common pattern in this part of the state, especially in smaller communities. Possibly it reflects a degree of self-confidence that permits the resident to assume the financial and personal risks associated with such a decision. Possibly it reflects the independent spirit that permitted our residents to break away from the traditional training environment of the academic center and come here for their residencies.

Many of our residents remained here for less than three years. National statistics show that about twenty-five percent of first year internal medicine residents plan careers in other fields.[2] The information that we have about our impact on these residents is not as clear as that which we have on our three-year graduates. We can feel certain that we have provided them with a valuable experience, but it is difficult to know what effect this has had on their selection of practice pattern or location. The fact that over half who have completed their training have established practices in the state suggests that our efforts with these trainees are compatible with AHEC goals.

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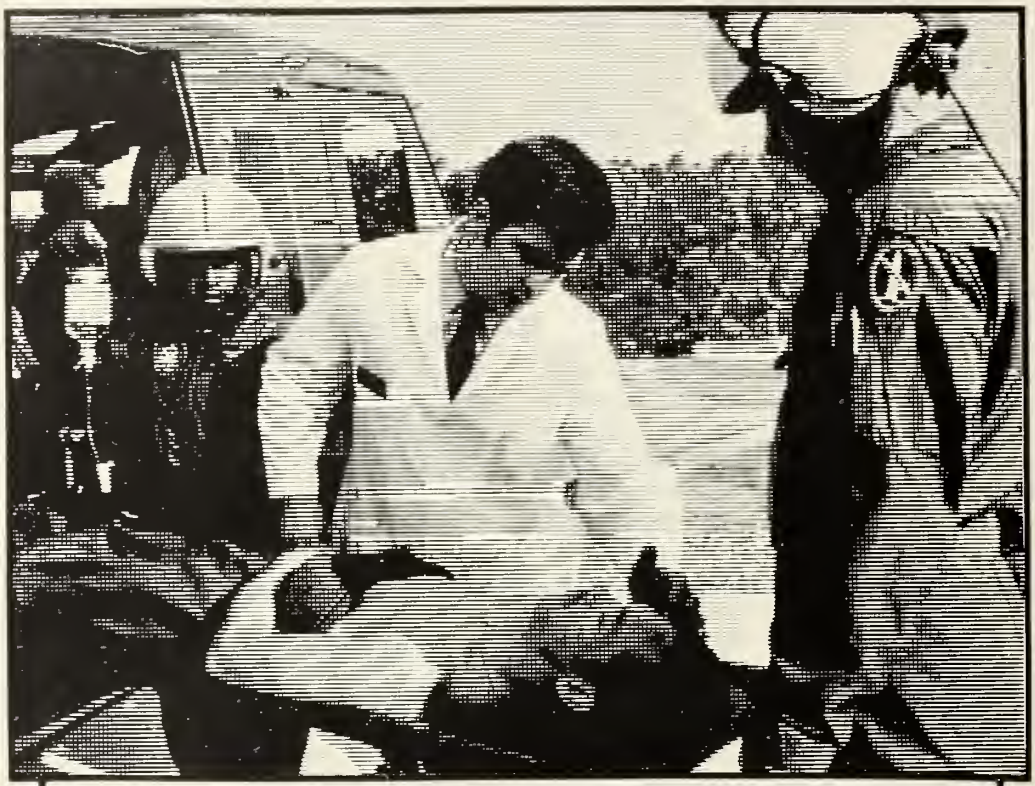
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References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
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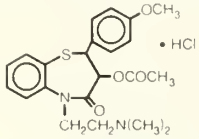
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DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia, and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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Cyrano De Bergerac Would Have Loved 1,1,1-trichloroethane

Ronald B. Mack, M.D.

• *If your secretary is making more typos and enjoying them more as well, check your correction fluid supply.*

PROBABLY one of the greater perquisites of being a professional is that you can utilize the services of a secretary. I frankly would be lost without mine (are you listening, Debbie Weatherman?). Lately some of you may have noticed that your secretary has been making more typing mistakes and seems to be enjoying the errors and, furthermore, the more typos the more happiness. Possibly she or he is "turning on" to the typewriter correction fluid which has become another in the long list of substances that can cause a "high" (in some instances you get so high you touch the sky and never come down again). This form of self destruction is becoming popular among sophisticated teenagers as well.

Typewriter correction fluids, e.g., Wite-Out, Liquid Paper, etc., are chlorinated solvents that are inexpensive and very available at your local supermarket, drug store, office supply, discount store or variety store. The major ingredients of these fluids, for the purposes of our discussion, are 1,1,1-trichloroethane, AKA methyl chloroform and henceforth referred to here as *TCA,* and trichloroethylene — TCE. You might recall that in the past both of these chemicals have been utilized as general anesthetic agents but have subsequently been replaced by safer chemicals.

The inhalation of volatile substances to produce a "psychedelic" experience has certainly been much in evidence in this post World War II Age of Aquarius. That euphoria can be by the induced inhalation of chloroform, carbon tetrachloride perchloroethylene, toluene, gasoline, or benzene is yesterday's news. It seems that today's thrill seekers are searching for newer and better ways to alter their consciousness. Does it not seem to you that man has attempted to undergo changes in his/her mental status throughout history by using chemicals? Usually the drug was taken orally, but no body orifice has remained chaste as even cursory reading of the history of medicine can attest.

Possibly the ear has remained the most virginal in terms of accepting chemical substances that can produce general as opposed to local deviations of homeostasis. My absolute favorite ear story involves the "murder most foul" of Hamlet's father by the young Danish prince's uncle-stepfather, Claudius. If you recall the story, Hamlet's father (in the form of a ghost) explains to our protoganist that he was killed by the introduction of the "juice of the cursed hebenon" into his ear which subsequently caused his premature demise. How could Shakespeare have made up such a story? Was this the science fiction of that era? According to a recent article,[1] Shakespeare may well have known about the work of Bartolommeo Eustachio who published his classic studies almost a half century before Hamlet was first performed on the stage. Apparently chronic purulent otorrhea was relatively common in Elizabethan times and furthermore it is strongly alleged that medical personnel of those times knew that middle ear fluids could drain into the pharynx and thus a substance, toxic or otherwise, could be instilled into the external auditory canal, transverse a perforation of the tympanic membrane, enter the pharynx by way of the eustachian tube and then be swallowed and absorbed via the GI tract. It is further alleged that the "cursed hebenon" was actually henbane, obtained from the plant of the hyoscyamus species. For those of you who have spouses or co-renters who bear evil thoughts toward you I suggest you invest in a pair of ear plugs — is nothing sacred anymore?

But I digress — probably because I have made so many mistakes typing this that I have "used" one half bottle of typewriter correction fluid. TCA can be readily absorbed via the skin, GI tract, and lungs; it is very very volatile and is absorbed most significantly through the respiratory system. If you accidentally or purposely swallow this solvent you can experience nausea, vomiting, abdominal pain, and diarrhea within 30-60 minutes along with confusion, agitation, amnesia, lethargy and dizziness not to mention ventricular arrhythmia and death. An important clinical clue is the odor of hydrocarbons detected in the effluvium from the gastrointestinal tract. Dermal contact with these chlorinated solvents can potentially cause systemic adversities but that is unlikely. First and second degree burns can occur, however, as can various irritating dermatitides and staining of the skin.

For most health care professionals who encounter a patient undergoing a toxic episode resulting from TCA or TCE or the like, it will most likely be due to the patient's *inhalation* of one of these chemicals. It is entirely possible that your first encounter with such a patient will be to

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

pronounce him or her dead. These substances are "sniffed" by the user to obtain a state of euphoria but larger acute inhalations proceed to dizziness, weakness and then progress to unconsciousness, seizures, as well as respiratory depression and cardiovascular collapse. In addition to these major insults, the toxins very adversely affect the myocardium by causing a sudden release of catecholamines which may then predispose the heart to fatal dysrhythmias. It should be noted here that people who inhale euphoriants such as typewriter correction fluids do so by several methods: there are the **"huffers"** — who spray or pour the liquid onto a cloth which is then placed near the mouth or rolled into a tube and inhaled; the **"baggers"** — this method is used by the cognoscenti who place the substance to be inhaled into a plastic bag or other container while placing the open end of the bag over the head or face and breathing in the vapor. This method quite obviously lends itself to producing suffocation. Finally there is the more mundane user, known as the **"sniffer,"** who merely inhales the vapor by placing his/her nose over the opening of the container. The inhalation of solvents, such as trichloroethane, can lead to the "sudden sniffing death syndrome."[2] In this syndrome the act of inhaling the solvents plus exercise or stress causes a release of catecholamines which apparently potentiates the adverse effects of the inhalant on the myocardium resulting in severe cardiac arrhythmia and death. (I recently saw an intern die from the "sudden sniffing death syndrome" after asking one of his teenage patients in the clinic to remove his "sneakers.") A typical scenario of such an ignoble demise could be something like this: At midmorning you admonish your secretary for fouling up your appointments beyond all recognition — (known as FUBAR) — as well as producing more typos per square inch than usual. Your tirade causes your secretary to seek solace; she takes several "sniffs" of her typewriter correction fluid hoping to induce an euphoric state and assuage her feelings of incompetence. She begins to re-type the data requested and this time the old typos are corrected but untold new ones appear, like mushrooms after a rain storm. You explode in fury and question your secretary's parentage, IQ, hat size, etc. The humiliated employee appears quite anxious at this point and runs to the rest room only to collapse and die in the 3rd stall.

It is not always easy to diagnose a typewriter correction abuser. Of course it helps to know if the patient has a history of "sniffing" similar substances in the past. It most certainly helps you to make the diagnosis if the patient's breath smells like hydrocarbons and if there are opaque stains around the nose, hands, and clothing in an obtunded patient.

Assuming you are confronted by a patient who gets involved with one of these inhalant solvents and is still alive, what can you do to help? The treatment is essentially supportative; there are no "magic bullets" for this problem. The patient should be placed in a quiet nonthreatening environment in an effort to reduce the risk of further catecholamine release. Give oxygen if the patient is hypoxic and whatever you do, *do not give sympathomimetic drugs* such as isoproterenol or epinephrine. If you administer such a medication they may say of you "the patient was at death's door and the doctor pulled him through" — the wrong direction unfortunately. Beta blocking agents could be used to offset ventricular arrhythmias should they arise. Diazepam, given intravenously, is advised for seizures.

Why would anyone want to shove stuff up their nose on purpose? I don't know about you, but I don't mess with my nose — it's off limits — taboo — even for fingers. Apparently, inhaling 1,1,1-trichloroethane causes an euphoric state similar to alcohol-induced inebriation. Hallucinations may occur. The effect is often quite transitory so further inhalations are employed. I suppose having a big nose helps. Cyrano De Bergerac (the hero of the play by the same name, written by Edmond Rostraud[3]) probably had the biggest beak in modern literature. Cyrano was a "gallant soldier, brilliant wit, remarkable swordsman and a tragic poet but had the face of a clown." Early in the play his nasal appendage is described as follows, "My lords, there is no such nose as that nose — you cannot look upon it without crying, Oh, no, Impossible! Exaggerated!" Then you smile and say, "Of course — I might have known; presently he will take it off." Well, the nose did not come off, but Cyrano could have taken one snort of trichloroethane and had a world class "high."

The only real antidote to this problem is to buy your secretary a word processor.

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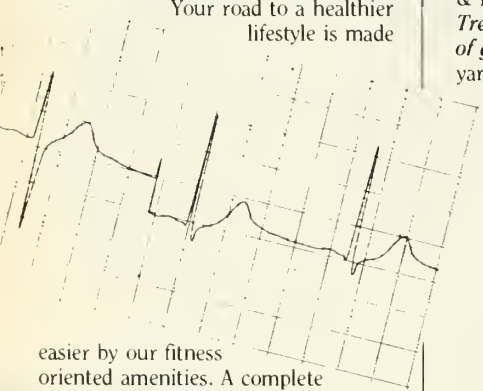
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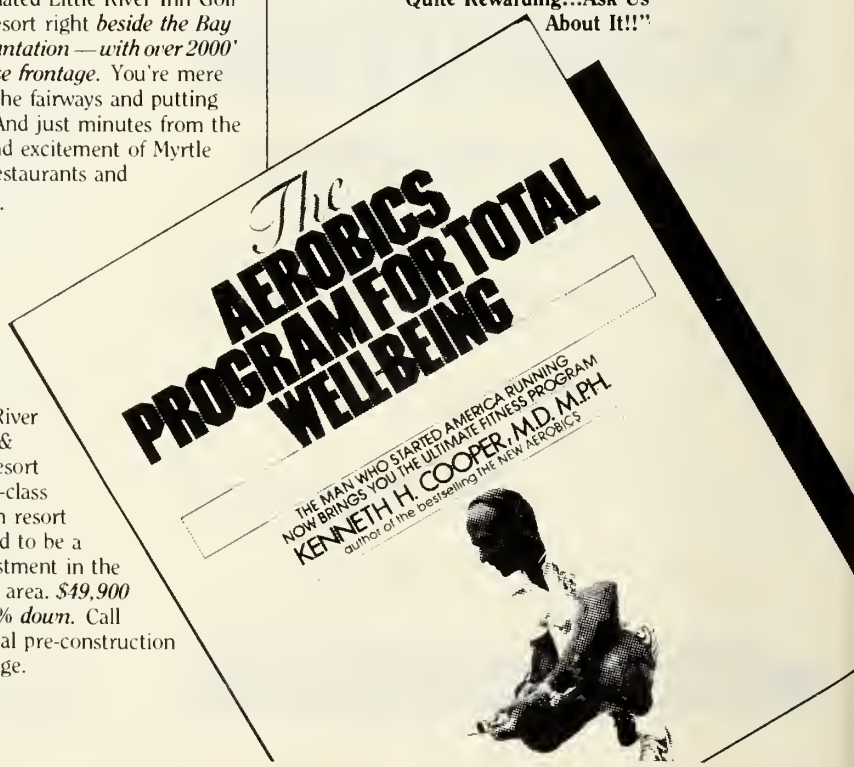
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Talking With Your Retirement Plan Advisor: Overcoming the Language Barrier

Walter R. Rogers, Jr., J.D. and Jennifer M. Dibble, J.D.

I. Introduction

Your retirement plan advisor is, or should be, an expert. Like all experts, he uses a specialized vocabulary for his technical descriptions. Just as physicians try to phrase advice in language patients can understand, good retirement plan advisors try to explain retirement planning in language clients can understand. However, the good intentions of even the best advisors often fall victim to time pressures. As a result, a client may adopt a retirement plan well suited to his needs but may also be left uneasy about how the plan works or why he chose it over other alternatives. We hope to help you overcome the language barrier posed by retirement plan advisors' specialized vocabulary by providing a glossary of some common qualified retirement plan terms you are likely to encounter.

II. Types of Qualified Retirement Plans

A. "Qualified" Retirement Plans.

"Qualified" retirement plans meet certain tax law requirements and therefore qualify for special tax treatment. The requirements for qualification are numerous, but they are grounded in certain basic policies. The terms or operation of a qualified retirement plan cannot unduly favor officers, shareholders or highly-compensated employees. This policy underlies the requirements that officers, shareholders or highly-compensated employees (sometimes called the "prohibited group") cannot enter the plan sooner, receive a higher percentage of pay as benefits or have a higher percentage of pay contributed to the plan, or become entitled to their benefits faster than other employees. Another major policy is that employees must know their rights under plans. This policy underlies the requirements that plans must be written, must be communicated to employees, and must contain definitely determinable benefits.

In return for meeting the tax law requirements, a qualified retirement plan receives several tax advantages. First, the employer who contributes funds to a qualified plan can deduct those contributions, within limits, from the employer's income for the year of the contribution. Second, as the retirement plan funds earn income, the increase in the funds is not taxed but accumulates tax-free until distribution. Third, the employee is not taxed on the contributions made on his behalf by the employer until the employee receives funds from the plan. Fourth, certain plan distributions may qualify for capital gains or income averaging tax treatment.

The following illustration shows why many physicians find qualified retirement plans attractive. The illustration compares Practice A which does not have a plan with Practice B which has a simple qualified defined contribution plan. Practice B contributes an amount equal to 10% of each employee's compensation to its plan and pays the rest of its income out in salary or bonus. After subtracting tax at an assumed effective rate of 35% from each physician's income, the physician's net increase in wealth is larger in Practice B than in Practice A. The physician in Practice B also has a smaller current income tax liability and provides a retirement benefit for his staff. Of course, eventually the physician in Practice B will pay income tax on the distribution he receives from his plan, but in the interim he enjoys the benefits of tax deferral.

	Practice A	Practice B
Income of Practice	$200,000	$200,000
Salaries and Bonuses		
Physician	185,000	166,818*
Nurse	15,000	15,000
Contribution to Plan		
For Physician	-0-	16,682
For Nurse	-0-	1,500
Physician's Benefit		
Salary and bonus	185,000	166,818
Less income tax	(64,750)	(58,386)
Plan contribution	-0-	16,682
Benefit	$120,250	$125,114

* The physician computes his compensation by subtracting fixed costs (nurse's salary — $15,000 and plan contribution for nurse — $1,500) from practice income ($200,000). Since the plan is a 10% plan, the result ($183,500) is 110% of the physician's compensation. Therefore the physician takes home (usually as a combination of monthly salary and year-end bonus) $166,818 (subject to tax) and contributes $16,682 to the plan on his own behalf.

Of course, in order to benefit from a qualified plan, the physician in Practice B must be able to give up the immediate use of amounts contributed to the plan. This is why retirement advisors look at a physician's current cash requirements to determine how much deferral he can afford.

B. "Defined Contribution" Plans.

A "defined contribution" plan is a type of qualified plan which states the amount that the employer will contribute to the plan on behalf of employees each year. The employer's

From the law firm of Smith, Anderson, Blount, Dorsett, Mitchell & Jernigan, Box 12807, Raleigh 27605.

contribution is allocated among the employees' "accounts" according to a formula in the plan. An employee's "account balance" consists of his share of the employer's contributions to the plan (and the investment return on those contributions), any contributions the employee makes to the plan, and a pro rata share of amounts forfeited by other employees who leave employment before being entitled to some or all of their account balances. An employee's retirement benefit from a defined contribution plan is his account balance at retirement.

Tax law imposes limits on the amount which may be added to an employee's account annually under a defined contribution plan. An employee's account can receive no more than the lesser of $30,000 or 25% of the employee's compensation each year from employer contributions, certain employee contributions, and forfeitures. The conventional wisdom is that a defined contribution plan is best for younger employees who stay with the employer for a substantial period of time. This is because annual contributions made over a long period of time (and the investment return on those contributions) can result in large account balances. A defined contribution plan is also relatively simple to administer.

1. "Money purchase" plans.

A "money purchase" plan is a qualified defined contribution plan that states in definite terms the amount that an employer will contribute to the plan each year.

2. "Profit sharing" plans.

A "profit sharing" plan is a defined contribution plan to which an employer contributes a percentage of profits each year. Some profit sharing plans state the percentage of earnings and profits that the employer will contribute each year. Other profit sharing plans permit a year-to-year determination of the amount of profits an employer will contribute. Obviously, an employer who is uncertain of its ability to contribute to a qualified retirement plan each year will find the flexibility of a profit sharing plan appealing. The tax law generally restricts the employer's deduction for amounts contributed to a profit sharing plan to 15% of employees' compensation, which is lower than the limit for employer deductions for contributions to other types of plans.

3. "Cash or deferred" or "401(k)" plans.

A fairly recent addition to retirement planning vocabulary is the "cash or deferred" or "401(k)" plan. A 401(k) plan is actually a type of profit sharing plan. Cash or deferred refers to the choice given an employee to defer income by having the employer contribute a percentage of the employee's pay to the profit sharing plan or to receive it as current cash compensation. Section 401(k) is the section of the Internal Revenue Code that permits such a plan. A 401(k) plan can be a "salary reduction" plan in which an employee reduces his current stated salary by electing to defer some of it. Another type of 401(k) plan is a "bonus plan" which gives an employee the choice to receive or defer amounts paid in addition to regular salary.

The attraction of a 401(k) plan is the flexibility it gives employees. Frequently employees have different cash needs. Some can defer the maximum permissible contribution until retirement while others need current cash. However, a 401(k) plan is administratively complex. The higher-paid one-third employees cannot defer amounts in excess of a certain percentage of amounts deferred by the lower-paid two-thirds employees. In practice this means that unless many of the lower-paid employees elect to defer, the higher-paid employees cannot defer as much as they may wish.

C. "Defined Benefit" Plans.

A "defined benefit" plan is a type of qualified plan that states the amount a participant will receive from the plan at retirement. The employer uses the services of an actuary to calculate what contributions the employer must make to achieve the level of benefits promised each employee. The actuary makes assumptions about employment habits, mortality and return on investments. If the employer's experience differs from the actuary's assumptions, the employer will adjust the contributions to the plan accordingly. Thus, in contrast to a defined contribution plan, a defined benefit plan puts the risk of investment return and other variables on the employer.

The conventional wisdom is that a defined benefit plan favors older employees with a relatively short time to retirement. Such employees would not be able to accumulate much retirement capital in a defined contribution plan because of the limits on annual additions to such plans. However, an employee retiring at age 62 or older may currently receive at retirement from a defined benefit plan as much as the lesser of $90,000 per year or 100% of average compensation for the highest-paid three years of employment. To meet this benefit over a short period of employment the employer will have to contribute large amounts to the defined benefit plan each year, which is useful to an employer who wants a large tax deduction. A drawback to the defined benefit plan is its complexity, which makes its administration more expensive than that of a defined contribution plan.

Defined benefit plans differ according to the formulae used for calculating benefits. Some plans state that benefits will be a percentage of final average compensation while some calculate benefits as a percentage of an employee's highest annual compensation amounts. Others multiply a percentage of compensation times an employee's number of years of employment.

D. "Keogh" or "HR-10" Plans.

Before the Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA), tax law imposed special limits on qualified retirement plans for self-employed individuals such as sole practitioners and partners in a medical practice. Plans which covered self-employed individuals were known as "Keogh" or "HR-10" plans and were in many ways less attractive than corporate qualified plans. By 1982, Congress had realized that some persons who might otherwise operate as sole proprietors or in partnerships were incorporating under "professional association" laws just to avoid Keogh plan limitations. In TEFRA Congress eliminated most distinctions between Keogh plans and qualified retirement plans for corporations. Congress achieved this "par-

ity'' between Keogh plans and corporate plans by eliminating some of the Keogh plan restrictions and by extending other Keogh-like restrictions to all ''top heavy'' plans, whether corporate or noncorporate. (Our next article discusses ''top heavy'' plans.) Some distinctions between corporate and noncorporate qualified retirement plans remain, however, such as restrictions on borrowing from qualified retirement plans.

If you have not incorporated your practice and you have not had your qualified retirement plan reviewed since 1982, you should check with your retirement plan advisor to see if your plan is unduly restrictive. If you are debating whether or not to incorporate your practice, remember that although TEFRA eliminated most distinctions between corporate and noncorporate qualified retirement plans, corporations and corporate employees still receive special tax treatment with respect to certain other fringe benefits.

E. ''IRAs.''

Given the media blitz by brokerage houses and banks, everyone should know everything there is to know about individual retirement accounts or ''IRAs.'' One fact that people sometimes forget is that anyone who receives earned income can establish an IRA even if he is also covered by a qualified retirement plan. Thus, even if you have already established a qualified retirement plan in your practice, you can contribute a maximum of the lesser of $2,000 ($2,250 if your spouse does not have any earned income) or 100% of your earned income per year to an IRA. You can deduct the amount contributed to the IRA from your income in figuring your taxes, and the IRA's earnings accumulate tax free. Of course, there are restrictions on IRAs: one cannot withdraw the funds without penalty before age 59½; one must begin to withdraw funds by age 70½; one cannot invest IRA funds in collectibles; and one can only contribute cash to the IRA. However, unlike qualified retirement plans, the tax benefits of IRAs are available to you without the expense of having to cover your employees.

III. Plan Provisions

A. ''Participation.''

1. Coverage.

Once you have decided that the tax benefits of a qualified retirement plan are attractive, you need to determine its cost. Key to determining cost is determining how many of your employees your plan must cover, because not only must your plan cover you, but it must cover some or all of your employees. In order for a retirement plan to be qualified, it must meet one of three ''participation'' tests. Most physicians' plans meet the ''70% test.'' The ''70% test'' requires that the plan cover 70% of the employer's employees, except for employees who have not met certain age and service requirements. Employees whom the plan covers are called ''participants.''

2. Age and Service Requirements.

An employer can exclude employees from its qualified retirement plan because of their age or because they have not worked for the employer long enough, within limits. The maximum the employer can require, with one exception, is that its plan not cover an employee until the later of his twenty-fifth birthday or the anniversary of one year's employment. The exception is that an employer can require an employee to work for the employer for as long as three years before covering him if the employee is then entitled to all of his share of contributions made to the plan should he leave employment. Under a defined benefit plan, the employer can also exclude employees who begin working at an age within five years of the normal retirement age stated in the plan.

B. ''Vesting.''

What happens to a participant's share of contributions made to the plan if he leaves employment before retirement? In some cases, the participant may be entitled to nothing and ''forfeit'' his share of plan assets. The forfeited amount is divided among remaining participants and usually reduces the employer's contribution to the plan. Generally, however, a plan must provide that participants who leave after several years of employment but before retirement be ''vested'' in some or all of their share of plan assets. ''Vested'' means that those assets cannot be forfeited and allocated to anyone else but must go to the participant. The vested assets may be kept in the plan until the departing participant reaches retirement age or may be paid out to the participant before retirement age.

1. ''Cliff Vesting.''

There are many permissible vesting schedules, but physicians' plans must usually contain liberal vesting schedules. ''Cliff vesting'' provides that a participant is entitled to nothing until he works a certain period of time. After that time the participant is 100% vested. Since TEFRA, most physicians' plans using cliff vesting can require only three years of employment without any vesting. (Remember, if the plan requires that employees work three years before participating in the plan, they must be 100% vested in their share of contributions from the first year of participation.)

2. ''Graded Vesting.''

Another type of vesting is ''graded vesting.'' Under graded vesting an employee is entitled to a larger percentage of his share of contributions each year until he is 100% vested. Before TEFRA, the IRS found ''4-40 vesting'' acceptable in many physicians' plans. An employee would not be vested at all until the fourth year of employment. In the fourth year, the employee would be 40% vested. Another 5% vesting would be added each of the next two years and 10% vesting each of the following five years. In the eleventh year of employment the employee would be 100% vested. Now if you choose to use graded vesting, you may be required to use ''six year graded vesting.'' After two years of employment, each employee will be vested in 20% of his share of contributions and 20% will be added each following year. The employee will be 100% vested after six years of employment.

3. Employee Contributions.

Finally, an employee is always completely vested in any

Table 1.
Comparison of Non-integrated and Integrated Plans

a. Non-integrated Plan

Participant	*Compensation*	*10% of Compensation*	*Plan Contribution*
Physician	$150,000	$15,000	$15,000
Nurse	15,000	1,500	1,500
		Total Contribution to Plan:	$16,500

b. Integrated Plan

Participant	*Compensation*	*5% of $15,000*	*10.7% of Excess*	*Plan Contribution*
Physician	$150,000	$750.00	$14,445	$15,195
Nurse	15,000	750.00	-0-	750
			Total Contribution to Plan:	$15,945

contribution the employee makes to the plan. This includes amounts he elects to defer under a 401(k) plan. This makes sense because, after all, the employee could have received the amounts deferred in a 401(k) plan immediately as cash.

C. "Discrimination" and "Integration."

1. "Discrimination."

Qualified retirement plans cannot "discriminate." This means they cannot favor officers, shareholders or highly-compensated employees over the employer's other employees. The prohibition against discrimination does not mean that all contributions an employer makes on behalf of employees under a defined contribution plan or all benefits a defined benefit plan pays to retired employees must be equal. Rather, the law provides that as long as those allocations or benefits reflect a uniform percentage of each employee's compensation, the plan is non-discriminatory. Thus, the allocation formula in a qualified defined contribution plan can allocate $25,000 to a physician's account, representing 25% of his $100,000 annual compensation, and $2,500 to a staff member's account, representing 25% of the staff member's $10,000 annual compensation. Similarly, a qualified defined benefit plan may pay an annual benefit of $90,000 to a retired physician and $10,000 to a retired staff member representing 100% of the physician's and staff member's final compensation.

2. "Integration."

When retirement plan advisors speak of "integration" they mean the process of combining the Social Security system with the employer's qualified retirement plan. An employer with a qualified defined contribution plan can count contributions made to the Social Security system on behalf of an employee as if the employer made those contributions to the employer's plan. An employer with a qualified defined benefit plan can count the benefits an employee receives from the Social Security system as if the employer's plan paid the benefits.

Integration can be a cost-saving feature in a qualified retirement plan. Naturally there are many rules regarding how an employer can integrate a plan. In a defined contribution plan, for example, an employer can contribute a certain percentage of compensation under the "integration level" and a higher percentage (currently a maximum of 5.7 percentage points higher) of compensation over the "integration level." The "integration level" is any compensation cut-off point the employer chooses, although if the employer uses a higher integration level than the Social Security wage base (currently $37,800) the employer must adjust the difference in contribution percentages downward. Retirement plan advisors generally recommend an integration level for physician's plans at or slightly above the highest staff salary for maximum cost efficiency.

Integrating a defined benefit plan is more difficult and depends on the benefit formula in the plan. However, the theory is similar since it allows employers to integrate the benefits a retired employee will receive from the Social Security system with the benefits he will receive from the plan. For example, one type of integrated defined benefit plan allows an employer to "offset" the benefits its qualified retirement plan provides with the benefits the Social Security system provides. As a result, the employer can reduce its contribution to the defined benefit plan.

Table 1 compares a non-integrated defined contribution plan with an integrated defined contribution plan. The integrated plan has an integration level of $15,000 and 5.7 percentage points difference between the two contribution percentages. You can see that with an integrated defined contribution plan the physician can make higher contributions to his own account while reducing the overall cost of the plan.

IV. Conclusion

We have just taken a glance at the tip of an iceberg. We hope that a basic understanding of some of the more common qualified retirement plan terms will help you communicate more efficiently with your retirement plan advisor. Our next article will cover in more detail recent tax law changes in this area, including the changes requiring plan amendments many of you are or will be adopting before the end of this year.

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See important information on next page.

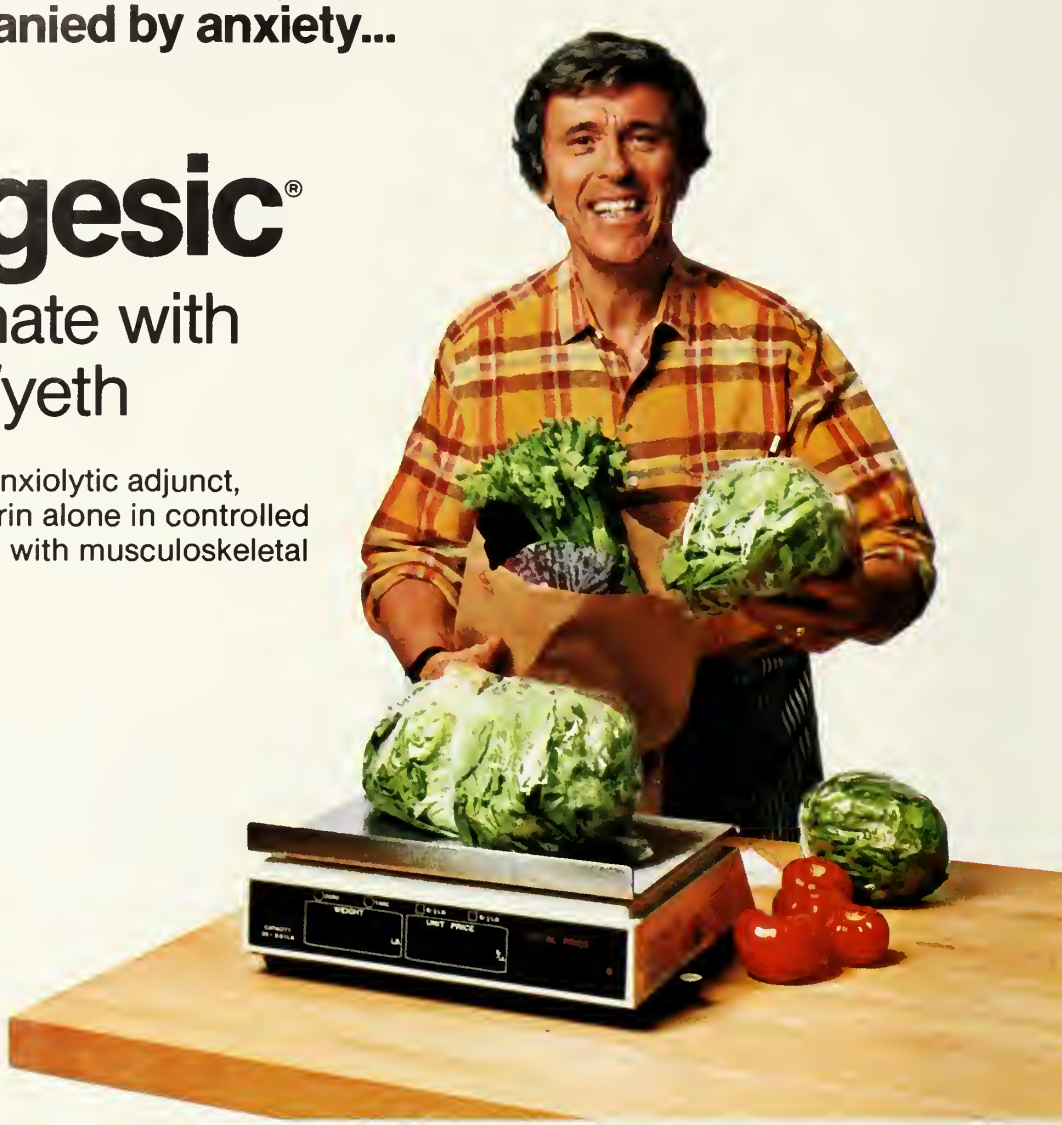


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(BRIEF SUMMARY)

DESCRIPTION:
Each tablet contains 200 mg meprobamate and 325 mg aspirin

INDICATIONS:
Adjunct in short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease. Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone. Effectiveness in long-term use, i.e. over 4 months, has not been assessed by systematic clinical studies. Physicians should periodically reassess usefulness of drug for individual patients.

CONTRAINDICATIONS:
ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria, allergic or idiosyncratic reactions to meprobamate or related compounds, e.g. carisoprodol, mebutamate, or carbromal.

WARNINGS:
ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE: DRUG DEPENDENCE: Physical and psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually, greater than recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms, e.g. anxiety, anorexia, or insomnia, or withdrawal reactions, e.g., vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinosis, and, rarely, convulsive seizures. Such seizures are more likely in persons with CNS damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation, symptoms usually cease within next 12- to 48-hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e.g. driving or operating machinery.

ADDITIVE EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION: An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlordiazepoxide, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug.

Meprobamate passes the placental barrier. It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS:
ASPIRIN: Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney; to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS:
ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS: Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity.

GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate/mebutamate and meprobamate/carbromal. Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC"): Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms.

DOSAGE AND ADMINISTRATION:
Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSAGE:
Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdosage produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole-blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal. The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported. Acute simple overdose (meprobamate alone): Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS:
0.5-2.0 mg percent represents usual blood-level range of meprobamate after therapeutic doses. The level may occasionally be as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdosage, such as stupor or light coma.

10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment. Some fatalities occur.

At levels greater than 20 mg percent, more fatalities than survivals can be expected.

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol): Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated. Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption.

HOW SUPPLIED:
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Physicians, Prescriptions and Prescription Drugs

John A. Ewing, M.D.

• *Physicians in North Carolina need to be cautious in their prescribing practices lest they contribute innocently to the State's growing drug dependency problems.*

CHARLESTON, South Carolina was selected for a 1984 AMA-sponsored conference on Prescription Drug Abuse involving representatives from eight southeastern states. I attended on behalf of the North Carolina Medical Society and learned much that I want to share with fellow physicians.

Size of the Problem

Mr. Roy Epps who is Chief of the Regulatory Branch of the North Carolina Department of Human Resources underlined the enormity of the problem when he told us that no less than 100,000 people in North Carolina have legitimate access to controlled substances. Annually, between 125 and 150 drug deaths occur in our State, 90% of these from prescription drug overdose. The "street drugs," such as cocaine and heroin, account for only 10% of such deaths. Those who know estimate that at least two hundred thousand dosage units of drugs are obtained illegally by forgery in North Carolina annually.

Cost of the Problem

Mr. Keith Bulla who is with the Drug Investigative Unit of the State Bureau of Investigation told us that even our blank prescription forms have value to criminals. He had made some interesting calculations. For example, a current problem is the diversion of phenmetrazine hydrochloride (Preludin) to the street. Big money is involved. He finds that, based on current street prices, a person who could persuade a physician to write a prescription for 60 tablets and, by shopping around, could accomplish this five days a week would have a profit of $240,000 at the end of one year. Such criminals exist out there and do come to our offices. One who specializes in hydromorphone hydrochloride (Dilaudid) and who has built up a relationship with a series of physicians can have a lucrative business. Bulla has calculated that such a criminal, seeing each physician approximately every six weeks, need only have duped 18 in order to get three prescriptions weekly for up to 100 Dilaudids. These tablets, on the street, will provide the criminal with an annual income of $780,000 after all expenses are taken care of!

Iatrogenic Drug Dependence

A recent JAMA survey showed that 1.6% of prescriptions involve drugs to combat anxiety that are still being taken by patients as much as seven years after they were originally needed. In some instances we should be educating our patients that drugs are not always the answer. With drug-dependent patients we should be promoting a program of gradual withdrawal.

Diversion

However, diversion of prescription drugs is the greatest problem. In this area, in addition to educating physicians about how they may be used, there are obvious needs for law enforcement.

An ex-criminal and ex-drug addict told us how he became disenchanted with the poor quality of heroin available on the streets of New York. He then became a professional "doctor shopper." To accomplish this he would dress well, be carefully groomed and ready to pay in cash. He said that some "soft touch" doctors were innocent, but could always be good for at least one prescription. He specialized in complaints of lower back pain and simulating the symptoms of a kidney stone. In addition to finding innocent doctors, he began to know of some who were willing to write a prescription for a fee. Another source was the pharmacist who illegally catered to drug abusers. From such sources this drug addict used to purchase Dilaudid tablets for $7.50 each and maintained his own habit by selling these on the street for $25 to $35 each. Again and again he saw physicians reaching for prescription pads after being fooled by him, instead of talking about the real problem of drug dependence and the need for appropriate treatment.

Physician Involvement

Speaker after speaker described the doctor who gets involved in prescription drug diversion as showing some specific characteristics: he may be dated, defiant (of government regulations), disabled, dishonest, distracted, duped, drugged or drunk. Obviously, the issue of the impaired physician is a subject in itself. But too many of us are easily distracted and duped under the pressures of hospital and office practice.

Countermeasures

Although some of the problems call for law enforcement, we as practicing physicians can reduce prescription drug abuse and diversion by exercising care and by seeing that office staff are aware of the problem and what should

From the Center for Alcohol Studies, UNC School of Medicine, Chapel Hill 27514.

be done. Even blank prescription pads are valuable and should not be left where they can be easily stolen. They should never be used for penciled memoranda or notes that can be erased. The actual amount of medication prescribed should be written out in words as well as in numerals. Pads should not be left in examining rooms, office areas or in bags or cars where they can easily be picked up. Obviously, prescriptions should be written in indelible ink and prescription blanks should never be signed in advance.

Manipulative Patients

Addicts who will try to dupe us will often claim physical problems, particularly illnesses having symptoms of severe pain which are generally treated with narcotics. Some will feign psychological problems, complaining of insomnia, fatigue, depression, anxiety or stress when stimulant drugs or depressants are desired rather than analgesics. Some will use deception including theft, forgery or alteration of prescriptions, often requesting refills prematurely. They will claim that the medicine was lost or stolen. Some have been described as even employing coercive tactics such as threats of physical or financial harm, bribery, or citing influential families or friends to obtain the medications they desire. Common characteristics of drug-seeking behavior include dramatic but vague complaints; subjective complaints without confirming objective signs; presentation of a self-diagnosis and naming of a specific medication desired; showing no interest in confirming a diagnosis or undertaking other forms of treatment and showing lack of interest in keeping appointments for referrals or diagnostic tests. When encountering such a patient we should maintain a strong professional control of the situation and look upon him or her as having a serious illness, namely, drug dependence. Discussing specialized treatment programs is indicated.

Plans in North Carolina

During the meeting in Charleston each state had caucuses to discuss state-wide responses to the problem of prescription drug diversion. Acting as spokesman for the North Carolina group, Mr. Steven L. Hicks, Deputy Director of Alcohol and Drug Abuse Services in the Department of Human Resources has recommended to Governor Hunt the appointment of a 15 member steering committee to address the problem. We hope such a committee will plan a North Carolina Conference on Prescription Drug Abuse, will discuss appropriate responses to the impaired professional who is contributing to the problem of drug diversion, will use the media to stimulate public awareness of the problem, and will focus on the education and training of professionals who can contribute their share to reducing the problem of drug diversion.

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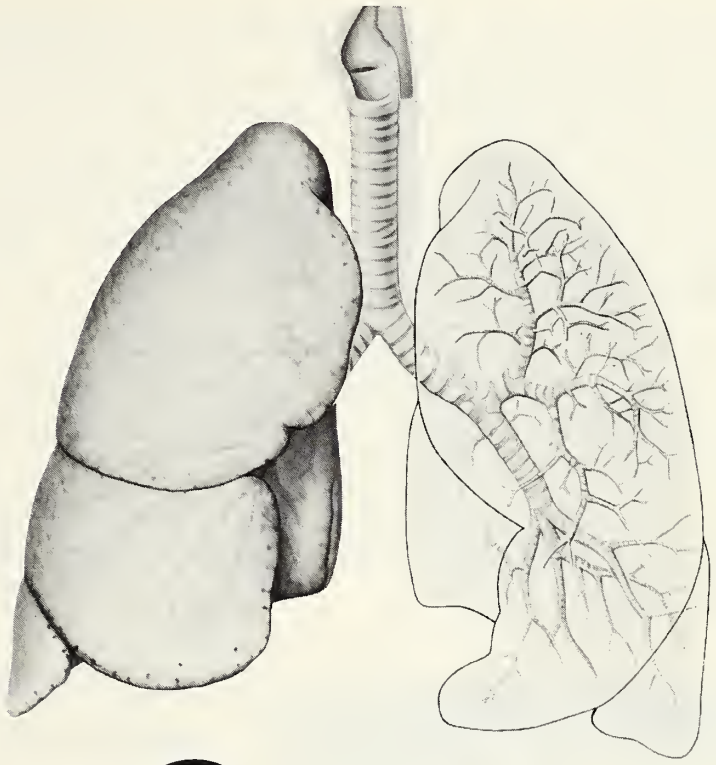
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Brief Summary Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets, but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy — Pregnancy Category B — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbiliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note: Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Bulletin Board

Continuing Medical Education

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IN STATE

October 13-14

Radiology Mini-Course in Abdominal Imaging
Place: Durham
Credit: 10 hours Category 1 AMA
Info: Cindi Easterling, Box 3108, Duke University Medical Center, Durham 27710. 919/684-6878

October 17

Symposium on Critical Care
Place: Gastonia
Info: Linda Mauldin, Gaston Memorial Hospital, 2525 Court Drive, Gastonia 28052

October 17

Update on Hepatitis
Place: Sanford
Credit: 2 hours Category 1 AMA and AAFP
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage Street, Sanford 27330. 919/774-6518

October 24-27

Fall Seminar, American Academy of Clinical Anesthesiologists
Place: Asheville
Credit: 11 hours Category I AMA
Info: AACA, Knoxville, TN 37919-1691. 615/588-6279

October 26-27

Psychopharmacology: Practical Drug Treatment of Psychiatric Disorders
Place: Chapel Hill
Credit: 10 hours Category I AMA
Fee: $125
Info: Nancy Williams, Department of Psychiatry, UNC School of Medicine, Chapel Hill 27514. 919/966-4738

October 26-27

Advanced Cardiac Life Support Instructors Course
Place: Winston-Salem
Credit: 20 hours Category I AMA and ACEP
Fee: $250
Info: Earl Schwartz, M.D., Emergency Medicine, Bowman Gray School of Medicine, Winston-Salem 27103.

November 1-2

Current Topics in Urology
Place: Chapel Hill
Credit: 13 hours Category 1 AMA
Fee: $125
Info: Barbara Judd, 428 Burnett-Womack Building 229H, Chapel Hill 27514. 919/966-2571

November 7

Update: Infant Psychiatry
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101. 919/723-3571

November 11-14

Advanced Clinical Teaching Skills
Place: Rougemont
Credit: 20 hours Category I AMA and AAFP
Info: Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

November 28

Obstetrical Analgesia/Anesthesia
Place: Sanford
Credit: 2 hours Category I AMA and AAFP
Info: R. S. Cline, MD., Central Carolina Hospital, 1135 Carthage Street, Sanford 27330. 919/774-6518

December 4

Duke Tuesday
Place: Durham
Credit: 5 hours Category I
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

December 5

Tourette's Syndrome
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101. 919/723-3571

OUT OF STATE

October 12

Selected Topics in Pediatrics
Place: Norfolk, VA
Info: Jean E. Shelton, M.D., Children's Hospital of the King's Daughters, 800 West Olney Road, Norfolk, VA 23507. 804/628-3798

October 12

New Guidelines for Management of Non-insulin Dependent Diabetes
Place: Richmond, VA
Info: Kay Parrott, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

October 18-25

Review of Clinical Chemistry Seminar
Place: San Diego, CA
Credit: 40 hours Category 1 AMA
Fee: $315
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

October 20

Medical Malpractice Risk Management
Place Williamsburg, VA
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494
Fee: $75

October 20-27

4th Diving Accident and Hyperbaric Oxygen Treatment
Place: Grand Cayman, BWI
Credit: 26 hours Category 1 AMA, AAFP, ACEP
Info: Cindi Easterling, Box 3108, Duke University Medical Center, Durham 27710. 919/684-6878

October 22-26

Postgraduate Course in Diagnostic Imaging
Place: Bermuda
Credit: 25 hours Category I AMA
Fee: $495
Info: Jacqueline D. Wright, Box 3808, Duke University Medical Center, Durham 27710. 919/681-2711

November 2-3

Fifth Annual G.I. Assistant: Principles and Practice
Place: Richmond, VA
Fee: $95
Info: Kathy Martin, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

November 13

Divorce, Child Custody and the Family
Place: Johnson City, TN
Info: Sue Hutchinson, Quillen-Dishner College of Medicine, Johnson City, TN. 615/928-6426, ext. 204

November 14-17

Williamsburg Symposium on Perinatal Care
Place: Williamsburg
Credit: 12 hours Category I
Fee: $200
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

November 16

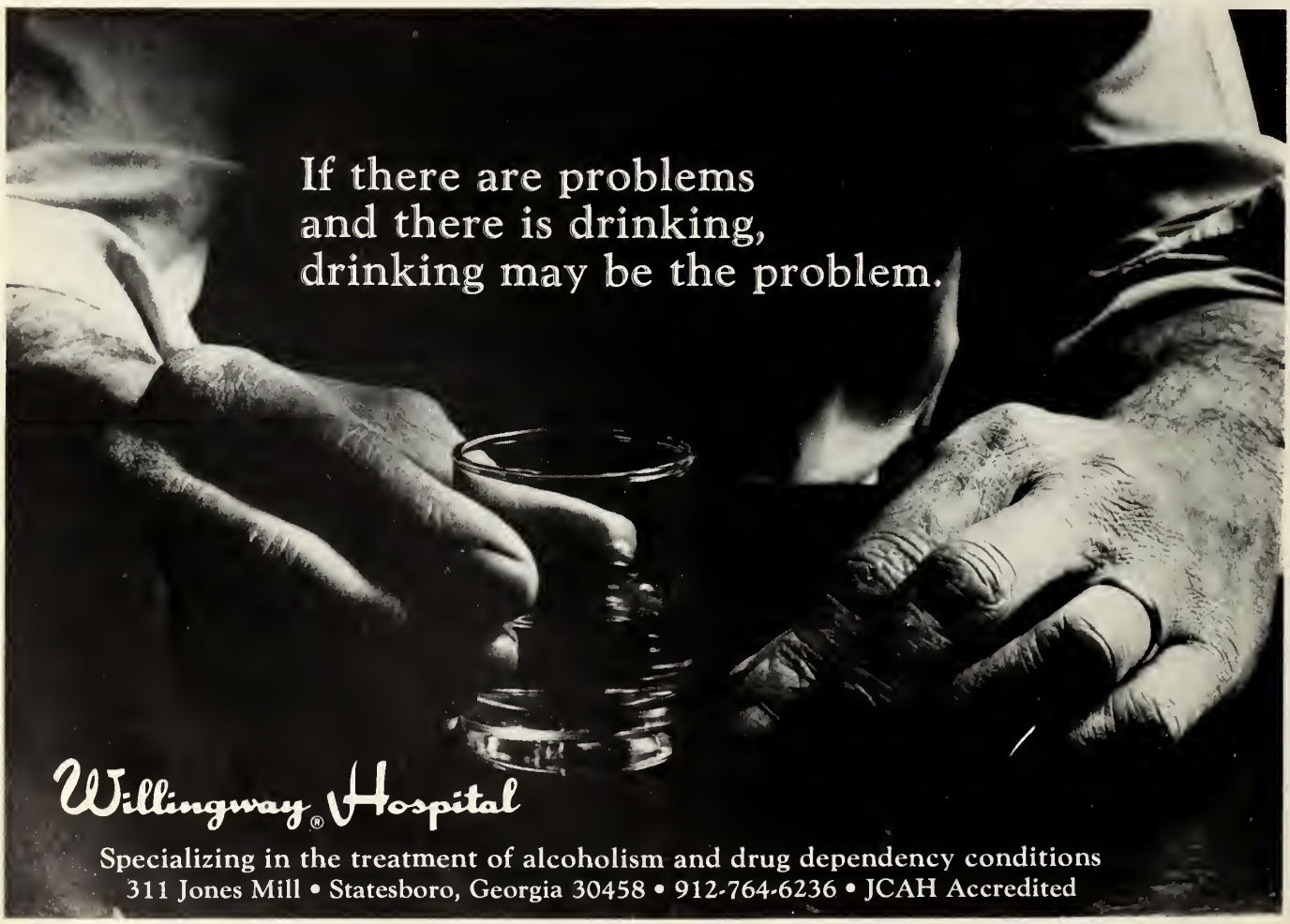
Update: Sudden Infant Death Syndrome
Place: Richmond, VA
Fee: $95
Credit: 7 hours Category I AMA, PREP, ACOG, AAFP
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

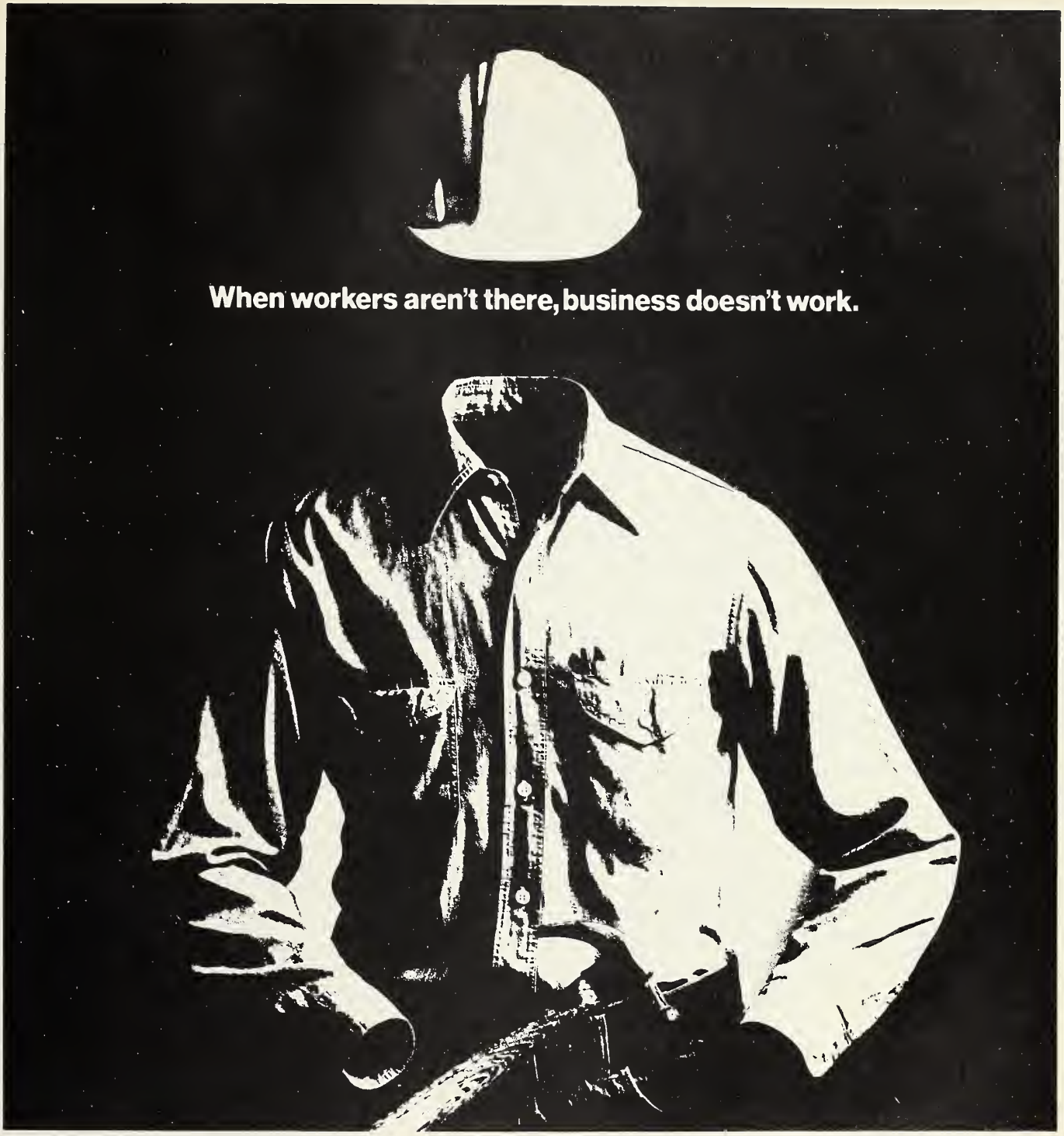
December 6-15

Review of Clinical Chemistry Seminar
Place: Snowmass, CO
Credit: 40 hours Category I
Fee: $315
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

Physicians Without Partners

A support group among divorced physicians is being formed. The first meeting will be in early October at the Center for Professional Well-Being, 5102 Chapel Hill Boulevard, Durham 27707. Phone: 919/489-9167. Physicians have unique issues to resolve in divorce. This group is being formed to provide a forum for discussion of the problems and feelings they confront. There will be a nominal fee.





Cancer strikes 120,000 people in our work force every year. Although no dollar value can ever be placed on a human life, the fact remains that our economy loses more than $10 billion in earnings every year that cancer victims would have generated. Earnings they might still be generating if they had known the simple facts on how to protect themselves from cancer.

Now you can do something to protect your employees, your company, and yourself... call your local unit of the American Cancer Society and ask for their free pamphlet, "Helping Your Employees to Protect Themselves Against Cancer." Start your company on a policy of good health today!

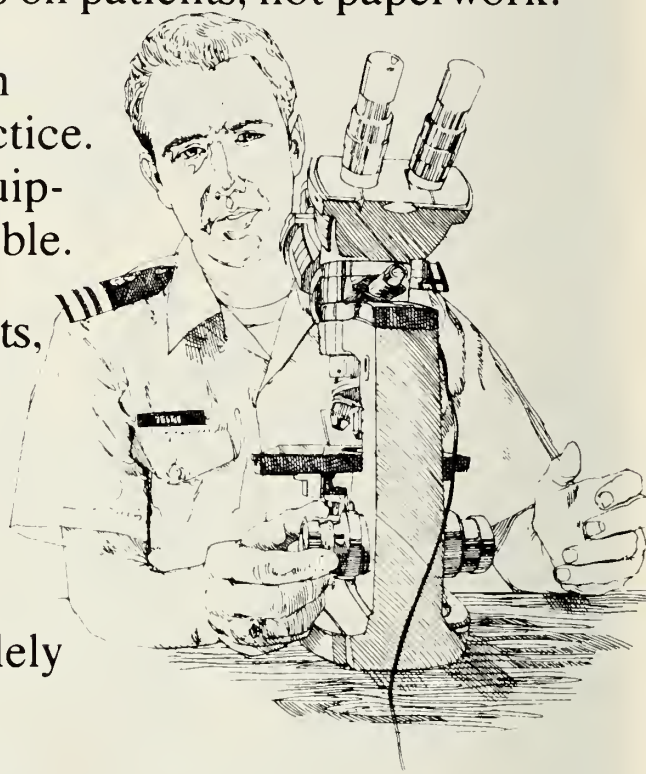
American Cancer Society

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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Letters to the Editor

Where Have All the Funtimes Gone?

I am a real fan of Ann Landers and read her column regularly. I have followed with particular interest the controversy concerning the working conditions of the housestaff in our teaching hospitals. This began several months ago with a letter from the mother of a resident physician deploring the exploitive nature of our training programs. She was particularly critical of the long periods on call which she felt left her son exhausted and unable to function adequately. A series of letters followed which either defended or attacked the system. One of these letters was from Dr. Jay Arena, professor emeritus of pediatrics at Duke University Medical Center, concerning his training years. Dr. Arena wrote, "Except for missing my wife, these were the happiest years in my life despite long hours, demanding responsibilities and almost nonexistent salary."

What Dr. Arena was saying was that the enjoyment of practicing medicine compensated for the lost sleep, limited social life, and even the lack of a living wage — quite a tribute to something so nebulous as "the joy of medicine."

I, too, found the years of residency training to be happy and rewarding ones, despite being paid almost as meagerly as Dr. Arena. What is the difference between now and then? Is the fun in medicine still there or have things changed so radically that the joy has been all but squeezed out?

Looking back thirty plus years, it seems to me that the basis of my satisfaction in those days was to finally be able to do the job that I wanted to do along with a group of people whom I liked and respected. During those housestaff years there was a spirit of camaraderie which accompanies a group of people who are working together toward a worthwhile goal. It can be compared with the spirit of the television series "MASH." There conditions were rotten, the job hours incredibly long, the work stressful and dangerous, but the spirit of cooperation toward the ultimate aim of saving the lives and limbs of our servicemen made it all worthwhile. At my residency hospital, it was fun to meet with friends in the dining room and discuss your interesting cases or the latest clinical pearl dropped on rounds or the goofs made by your rounding man, intern, or even yourself. There was a good deal of one-upmanship but this was largely carried out in a spirit of friendly jousting intended to stimulate rather than stifle your eagerness. In fact, probably more medical know-how was acquired at these impromptu sessions than at more formal rounds and conferences. The nights spent in the grim call rooms were usually compensated for by the challenge of managing that diabetic in acidosis or the patient in the emergency room with acute pulmonary edema. You might be tired and bored as you shifted from foot to foot on the third hour of ward rounds, but somehow you were aware that what you were doing was important and that you were being educated in the best sense of the word.

The rigors of the period were softened by the laughter. The young intern leaning over the bed of the lady who was unconscious from an overdose. "What did you take?" he shouts in her ear. No response. "What was the name of the medicine?" Only heavy breathing in answer. In desperation, louder, precisely articulated, "Was it a BAR-BIT-U-RATE?" Finally, a sluggish arousal. "NO, SECONAL." Or the morning report of the junior residents to the Chief of Medicine, a much respected physician and role model. While giving the report of the previous night's admissions, one of the housestaff notes that the Chief has on one brown and one blue sock. While others report, he agonizes as to whether to mention this to the Chief. At the end of report, he decides to do so. "You have one blue sock and one brown sock on, Sir." The cool response, "That's all right, John, I have another pair just like it at home." One morning, reporting to Dr. Eugene Stead about a physical finding on a patient: "Dr. Spleen, the stead was palpable." This is the glue which holds the pieces together.

As I look over my years of practice, I feel fortunate to be a part of this great profession and to have been able to grow and change with the times. I am especially appreciative of the opportunity to associate with my colleagues, men and women of the highest intellectual and moral character. We physicians quite naturally envision our relationship with our patients as a one-directional outflow of medical education, support, diagnosis and treatment — from us to them. The longer I am in the business, however, the more I realize that it is indeed a two-way street and that I have learned immeasurably from my patients. I am not talking about disease, but rather the numerous examples of human courage, fortitude, and sacrifice — the families who have given up all semblance of normal routine and livelihood to remain at the bedside day after day, night after night, ministering to a loved one — the sharcropper's wife who, through her strength of will and good sense, pulled her family through devastating economic and social hardship — the professor who for years cared for his wife, bedridden with multiple sclerosis — the vigorous, intelligent, witty ninety year old lady, who, when it was obvious that her life was fast fading, had one request of me, her physician, "Let me go, let me go." I often wonder if I could have tolerated the series of life's blows which I have watched my patients sustain and survive.

Changes there certainly have been over the years. The amount of information to be assimilated has exploded. The government has increasingly injected itself between doctor and patient. Housestaff members are now married, many have children, and therefore, have a divided loyalty. The intensive care units are keeping patients alive who, in my day, would have died. Their lives are sustained with minute-to-minute decisions on changes in dial settings and IV drug injections. Certainly, this increases the level of stress for the resident. Little seems to be left to the "Will of God" — everything seems to be up to our proper manipulations.

Despite the changes, the basic attraction of a career in medicine is still there — the interaction of one human being with another, and especially the privilege of ministering to the needs of another individual.

Where have all the funtimes gone? Nowhere, they're still very much alive.

Robert W. Willett, M.D.
2800 Blue Ridge Boulevard
Raleigh 27607

The editor remembers his first contact with Bob Willett. Sam Martin, the first chief resident I appointed at Duke and an excellent appraiser of talent, stopped me in the hall and asked me to accompany him to the resident's office. He had collared an outstanding third-year student and he hoped to persuade him to take his internship at Duke. I was equally impressed, and Bob more than measured up to our expectations. In one way, he went beyond. He was smart enough to persuade Hilda Pope, a budding bacteriologist, to marry him.

eas

Warmth Treatment of Nasal Obstruction Due to Antihypertensive Medicines

To the Editor:

I am a retired physician. I take medicines to control high blood pressure and gout. As a side effect of these medicines, I have had a continuing problem with nasal obstruction and infection. The problem has been worse in the winter than during milder weather.

Recently, I found that staying warm gave relief. If my nose is bothering me, I turn on the electric blanket and crawl into bed. Warming the legs and trunk is not a cure, but it does lessen the misery. Soon I feel better.

Of course, I know that using surface warmth as therapy is not original or any big discovery. But if you had spent as many restless nights as I have, and finally had found something simple which helped you breathe through your nose, you might be pleased. You also might regard this therapy as an improvement and want to share it with others.

Have any of our practicing profession made similar observations?

Albert D. Warshauer, M.D.
1608 East 5th Street
Greenville 27834

Kudos

To the Editor:

Just a brief word to tell you how much the men in our group, including myself, think the journal has improved since you have taken over at the helm. Please keep up the good work.

Austin T. Hyde, Jr., M.D.
312 South Ridgecrest Avenue
Rutherfordton 28139

We Help Alcoholics Recover.



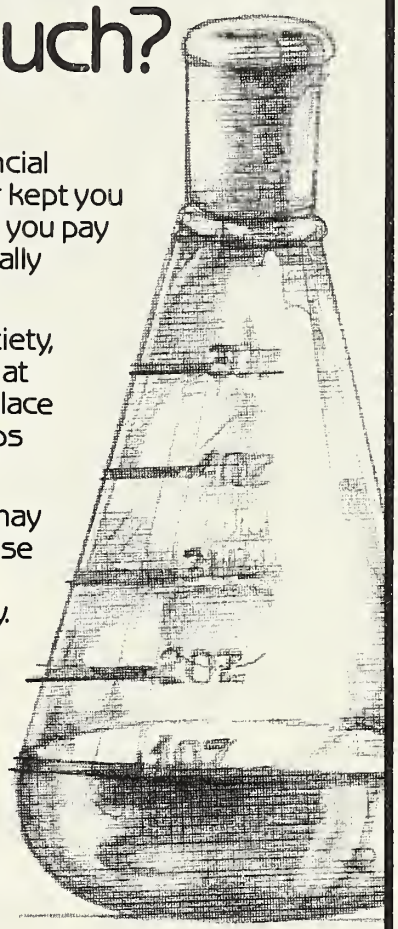
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Carolinas Hospital Alcoholism Program Services, Inc., **CONTACT Bridgeway,** Transylvania Community Hospital, PO Box 1116, Brevard, NC 28712, Tel. (704) 884-2100 **OR Pinehurst Treatment Center,** Moore Memorial Hospital, PO Box 3000, Pinehurst, NC 28374, Tel. (919) 295-7902 **OR CHAPS Baker Treatment Center,** Baker Hospital, North Charleston, SC 29405, Tel. (803) 744-2110.

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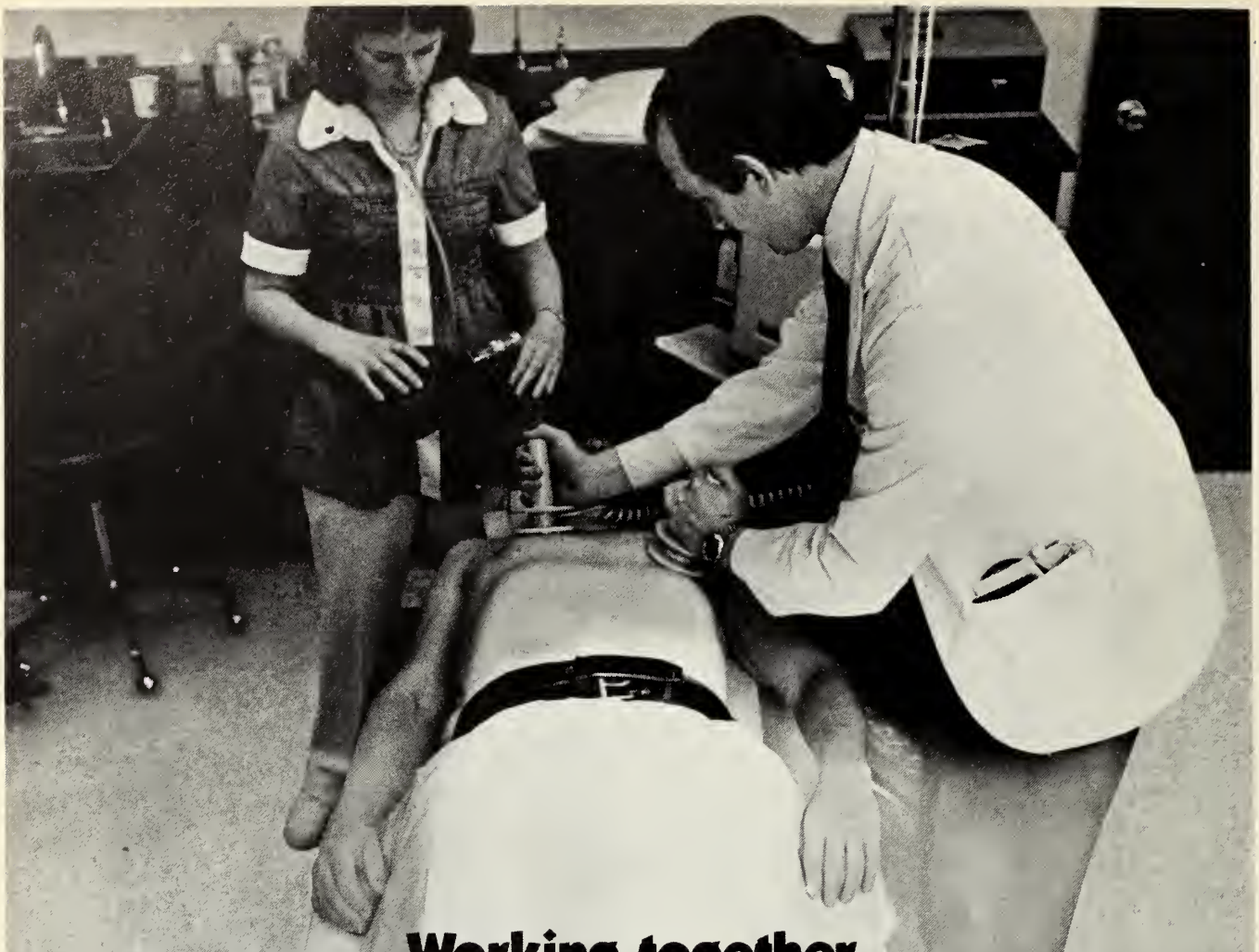
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Every day it becomes harder for her to see. Harder for her to walk. Harder to do the things she wants to do for her family.

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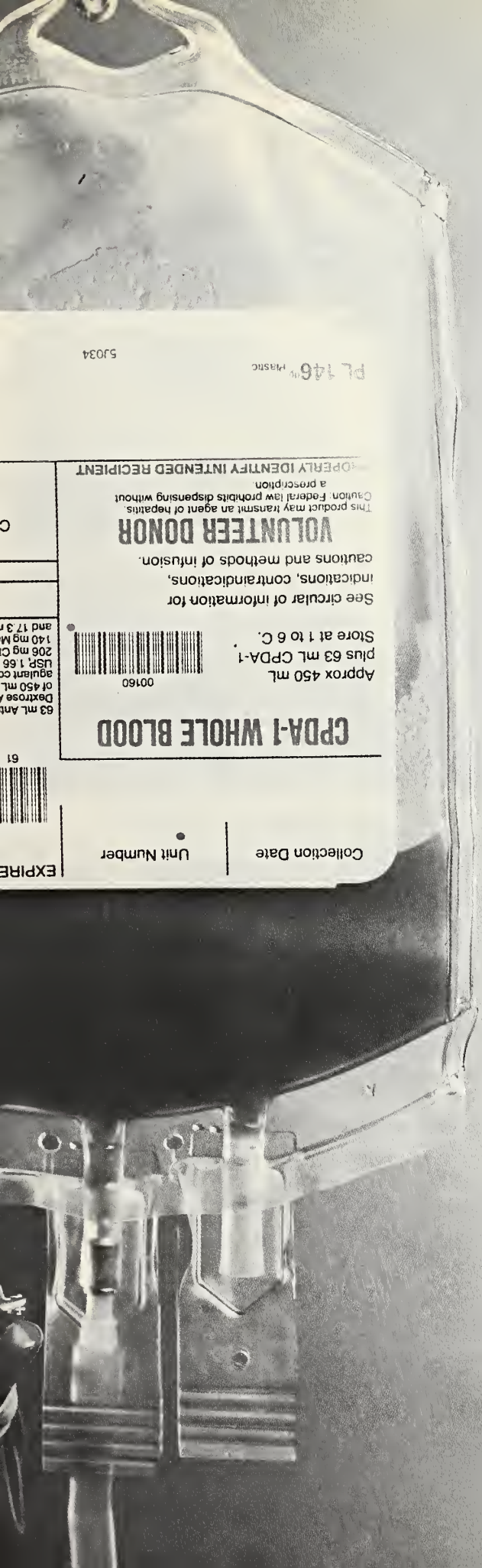
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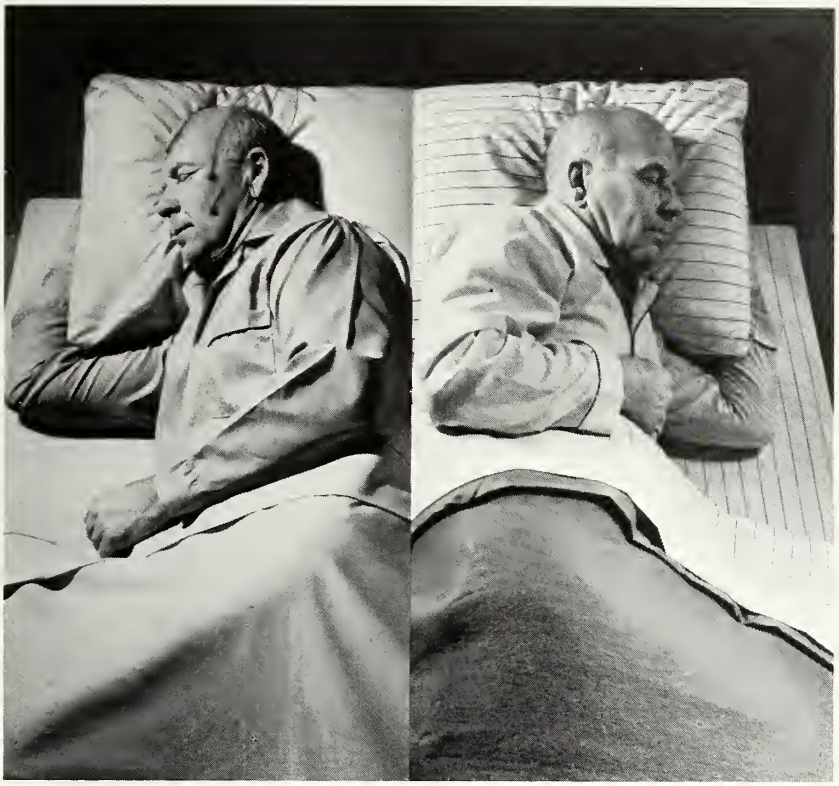
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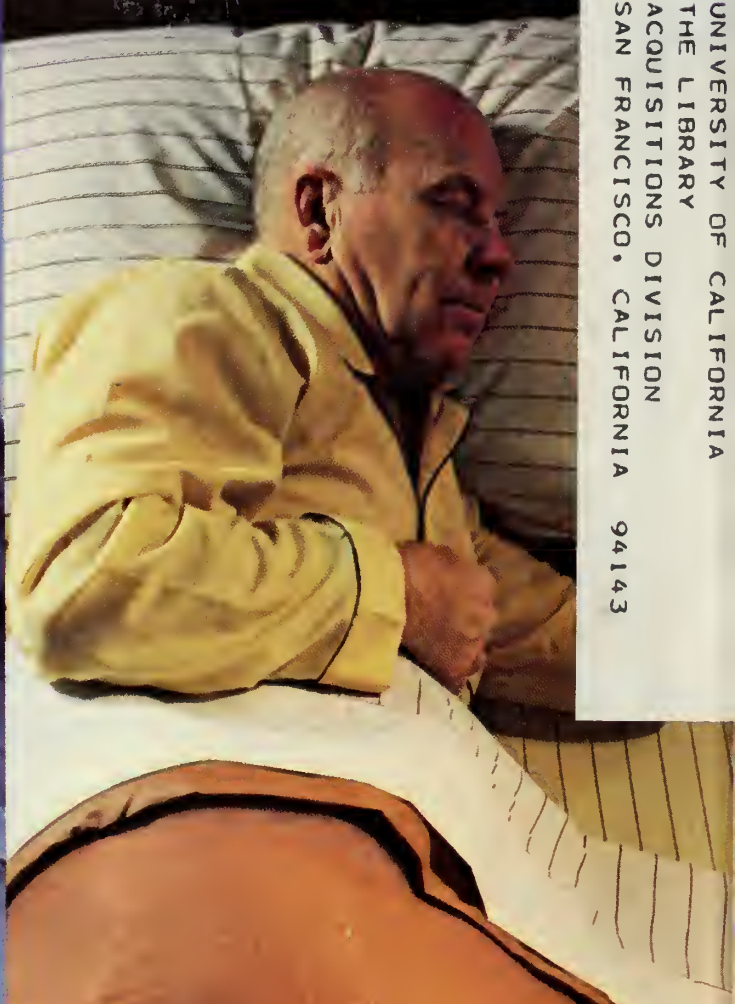
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Official Journal of the NORTH CAROLINA MEDICAL SOCIETY November 1984, Volume 45, No. 11

Trauma

Several articles devoted to the subject of the treatment of trauma — from orthopaedic and CNS injuries to seat belts and the use of helicopters (UNC's helipad is shown below) — have been collected by guest editor, H. J. Proctor, M.D.



Oleander Poisoning — page 729
by Ronald B. Mack, M.D.

Physicians' Forum — page 741
Public Health-Private Practice Overlap
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Source of Hair in a Pilonidal Sinus — page 735
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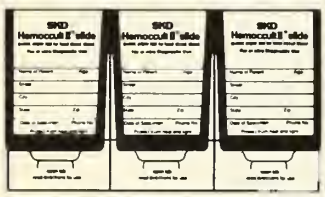
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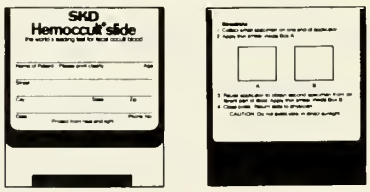
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Introduction

H. J. Proctor, M.D.

● *Introductory comments by the editor of this issue on trauma care in North Carolina.*

IT is indeed a pleasure to serve as unofficial "guest" editor for this issue of the *North Carolina Medical Journal* devoted to trauma. Since 1962 when I was a surgical intern at the North Carolina Memorial Hospital, I have had a unique opportunity to observe and participate in the evolution of trauma care in North Carolina. From 1962 when the emergency *room* was often referred to as the "pit," seldom frequented by senior staff members, has come the specialty of emergency medicine, the American College of Emergency Physicians, and the creation of the modern emergency *department* which has assumed a legitimate place in the hospital administrative hierarchy. Trauma victims are now delivered to emergency departments by well-trained EMTs or paramedics in well-equipped ambulances rather than by individuals with 26 hours of American Red Cross first aid using a hearse as a conveyance. The Office of Emergency Medical Services, categorization of hospitals, designation of trauma centers, standardized transfer protocols, radio communications and upgrading of ambulances have all evolved, enabled in large part by a beneficent legislature with a willingness to fund statewide programs and a willingness on the part of local governments to provide matching funds.

In this issue of the *North Carolina Medical Journal* much of the above progress is chronicled by Tom Harmelink, Chief of the North Carolina Office of Emergency Medical Services. There have been three Level I statewide trauma centers designated in North Carolina and a description of some of the activities of the University of North Carolina-North Carolina Memorial Statewide Trauma Center is included as an illustrative example along with articles illustrating specialized problems relating to orthopaedic injuries (Laurence Dahners, M.D.), and the approach to central nervous systems injuries (Michael Rosner, M.D.).

Several Level II trauma centers have also been designated. Frequently located with more rural surroundings, their unique problems in patient access, transportation, and emergency department care are addressed by Larry Lewis, M.D. of the Department of Surgery, East Carolina University.

A major mission of statewide trauma centers involves outreach educational programs. The two statewide trauma centers located at the University of North Carolina and Duke University have combined to develop and present such an educational program for physicians and nurses in community hospitals, described in this issue by Joseph Moylan, M.D., Chief of the Trauma Service at Duke University Medical Center. The North Carolina Committee on Trauma of the American College of Surgeons has been an extremely active professional organization as the article by Dr. Robert Youngblood illustrates. The Highway Safety Research Center, a part of the University of North Carolina Statewide Trauma Center, has been active in motor vehicle safety standards and the article by B. J. Campbell should be particularly interesting for the lay reader as well as the professional.

North Carolinians can be justly proud of the progress made in trauma care in North Carolina, where trauma is *not* "the forgotten disease of modern society."

From the Trauma Section, Department of Surgery, University of North Carolina School of Medicine, Chapel Hill 27514.

SCIENTIFIC ARTICLE

Emergency Medical Services in North Carolina

Thomas M. Harmelink

• *A history of EMS since 1966 – in North Carolina from 1973 to the present.*

TEN years ago it was referred to as ambulance services — today it is known as emergency medical services or more commonly as EMS. This change in terminology is symbolic of the significant developments that have taken place in the delivery of emergency medical care to the critically ill and injured. The emphasis today is on the establishment of a medical care delivery system and not simply on a transportation system offering a fast ride to the hospital.

The report, "Accidental Death and Disability — The Neglected Disease of Modern Society," issued in 1966 by the National Academy of Sciences-National Research Council is generally credited with bringing the nation's attention to the needless loss of life resulting from inadequate or absent emergency medical care systems. To some extent the problem is still as critical. Accidents are the fourth leading cause of death in North Carolina, as is the case for the entire United States, and the number one killer of those under the age of 35. The leading cause of death is heart disease, which claimed over 17,000 lives in North Carolina in 1982, over half of which can be attributed to acute myocardial infarction. These two major problems, along with many other critical illnesses, are being addressed through efforts at the state, regional, and local levels to establish emergency medical services systems.

Background and Structure

In North Carolina, activity was precipitated by the Emergency Medical Services Act of 1973 which established a statewide emergency medical services program. The Office of Emergency Medical Services was created in the Department of Human Resources and identified as the lead state agency for EMS activities. It was assigned regulatory responsibilities typical of those one comes to expect of a government agency, such as the certification of ambulance personnel and the inspection of ambulances. But, more importantly, it was given broader mandates to promote, encourage, and assist in the development of statewide, regional, and local emergency medical services programs. Along with the mandates came funding from the General Assembly to support the operational and developmental aspects of the program.

The legislation calls for an Emergency Medical Services Advisory Council to advise the Secretary of the Department of Human Resources on all matters pertaining to EMS. The Council is composed of representatives from paid ambulance providers, volunteer rescue squads, hospitals, local government, nursing, the medical community, the general public, and the state legislature. Early on, the Council adopted the following philosophy for the program which remains valid today:

(1) to foster regional services which are designed and operated in accordance with local initiative, regional needs and statewide standards and guidelines; and

(2) to provide supportive statewide programs to ensure that every medical provider is well trained, every emergency vehicle well equipped and properly operated, all components connected by effective communications, and every citizen within reach of high quality emergency medical care.

Basic to this philosophy and, thus, to the state EMS program, is the regional approach to establishing a comprehensive EMS system. Eighteen regions have been identified and a regional EMS council established in each to coordinate and develop the system on this level (figure 1). Each council is affiliated with the Lead Regional Organization (a council of governments or planning and economic development commission) in its region and has a membership similar to that of the State EMS Advisory Council. They are funded primarily by state funds and are responsible for identifying regional needs, establishing priorities within the region for funding, developing a regional EMS plan, planning and implementing regionwide projects, serving as a forum for resolving problems within their region and, in general, coordinating EMS activities.

The responsibility for providing ambulance service rests at the local level and, for all practical purposes, resides with the county government. Virtually all counties provide some level of funding to the ambulance services within their jurisdiction, usually in the form of direct operating costs or subsidies to volunteer and commercial providers. However, their actual involvement varies considerably, ranging from those who provide the service directly through a county ambulance service to those who take a much more passive, almost laissez-faire, approach. Evidence that county governments have realized a need to assert some control and influence over this public service is reflected in the fact that 30 have now enacted franchise ordinances to regulate EMS activity within the county and 52 have designated a county EMS director. Fewer, 16, have formally recognized the importance of considering more than just the ambulance service by establishing a local EMS council to coordinate all of the elements of the EMS system on a countywide basis. The types of organizations providing ambulance service have changed significantly since the

From the Office of Emergency Medical Services, Department of Human Resources, Raleigh 27605.

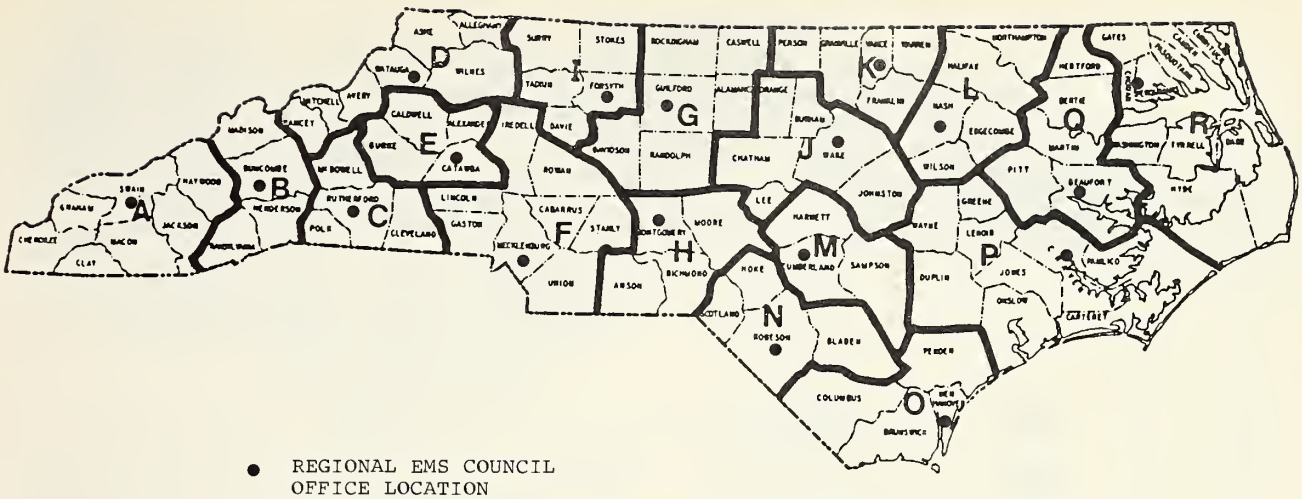


Figure 1. *Emergency medical services regions, June 1984.*

early 1970s as shown in table 1. In terms of numbers, most notable is the increase in the number of volunteer rescue squads from 205 in 1972 to 377 in 1984 to where they now comprise 73 percent of all providers versus 51 percent in 1972. To a large extent, they organized to fill the gap left by the departure of funeral home operators from the ambulance business. Funeral homes now make up less than 1 percent of the total. Also significant is the increase in government operated ambulance services mainly reflecting the commitment of local governments to ensure that EMS is provided to their community. Another trend resulting from the increased demand for EMS is the addition of paid personnel to volunteer rescue squads primarily to staff the service during the daytime hours. Some 23 of the 377 volunteer rescue squads have at least one paid EMT.

Systems Development

As with most aspects of health care, there are variations in the level of prehospital emergency medical care available across North Carolina. These can be broadly classified into two categories, basic life support and advanced life support, which can serve as a useful measure of the degree to which the EMS system, as a whole, is developed within a county and within a region. Basic life support refers to the provision of prehospital emergency care by personnel, such as EMTs, trained to perform emergency first aid and stabilization. The initiation of definitive treatment at the scene by personnel receiving orders from a physician in a sponsoring hospital is termed advanced life support (ALS). There are two levels of ALS in North Carolina (also referred to as mobile intensive care): (1) EMT-intermediate where the field technicians can start intravenous therapy and insert an esophageal obturator or esophageal gastric tube airway; and (2) EMT-paramedic in which they perform a wide range of medical procedures including the administration of certain drugs, defibrillation, and intubation.

Table 1

Types of Ambulance Service Organizations

	1972		1984	
	No.	Percent	No.	Percent
Funeral homes	105	26	4	—
Volunteer rescue squads	205	51	377	73
Governmental	24	6	67	13
Commercial	28	7	18	4
Hospital	12	3	19	4
Police and fire	24	6	15	3
Other	4	1	14	3
Totals	402	100	514	100

One of the early goals of the state EMS program was to ensure that basic life support services were provided statewide by personnel trained and certified as EMTs. This has been attained, and all ambulances operating in the state are staffed by at least one certified EMT. In achieving this basic minimum, the focus has shifted from providing transportation to the hospital to responding to the scene with well-trained personnel who can render immediate lifesaving care, stabilize the victim and then transport him safely to the hospital for definitive treatment. The lack of integration of basic life support services and their personnel into the medical care system, i.e., involvement with the medical community and the hospital, while significantly improved, continues to be an area of major concern.

As of June 1984, 47 counties have progressed beyond the basic level and provide advanced life support services to their citizens. Of these, 28 function at the EMT-intermediate level and 19 at the EMT-paramedic level (figure 2). Advanced life support programs cover 72 percent of the state's population, but only 40 percent of the geographical area. Further analysis shows that EMT-paramedic services are available to 32 percent of the population while EMT-intermediate services are provided to 40 percent. These figures point out that ALS programs have been largely established in the more populous counties which are most likely to have paid ambulance services. However, two counties with volunteer services are EMT-paramedic (Haywood and Orange) and were among the first in the state to achieve that status. In terms of ambulance providers, 22 — 17 paid and 5 volunteer — have personnel trained and functioning as EMT-paramedics and

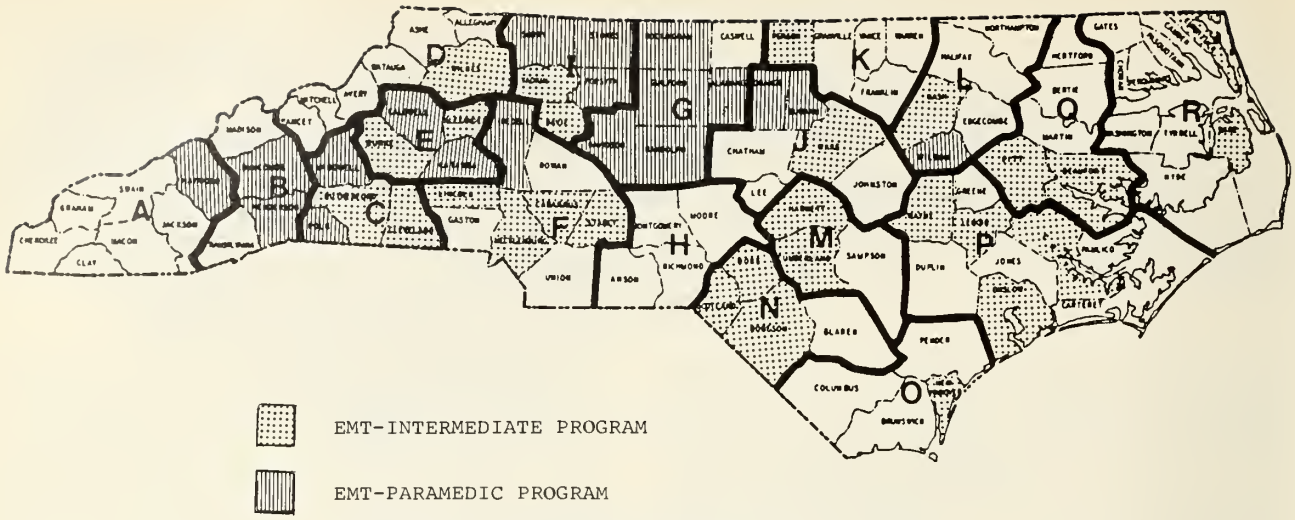


Figure 2. *Advanced life support programs, June 1984.*

53 — 23 paid and 30 volunteer — have personnel trained as EMT-intermediates. More rural counties and volunteer providers are realizing that the EMT-intermediate level is reachable and, in recent years, have made the commitment to upgrade their service to that level.

Training

Progress in North Carolina's EMS program has been most visible in the training of ambulance personnel (table 2). This can be attributed to the fact that it was one of the most deficient aspects of emergency care in the state and, consequently, has been the focus of the Office of Emergency Medical Services' efforts and resources, especially early on. The emergency medical technician training program has been established as the basic standard for ambulance personnel in the state, as it is nationally, raising the minimum training requirements from 30 hours to 81 hours. In reality, however, the average EMT course runs 110-120 hours which is consistent with the latest version of the National Standard EMT Curriculum. State statutes and regulations still recognize a category of certified ambulance attendant, requiring 40 hours of training. There are few ambulance attendants in comparison with EMTs, and most ambulances are staffed with a minimum of two EMTs. Prior to 1974, there were only a handful of EMTs in North Carolina, while in 1984 there are 16,028 holding current certification from the Office of Emergency Medical Services. An estimated 50,000 persons have now taken the EMT training course which is offered through the community colleges. Unique among health professionals, and a point of continuing controversy, particularly among many of the volunteers, is the requirement to take a state examination and be recertified every two years.

Table 2

Certified EMS Personnel

	1977	1980	1984
Ambulance attendants	1,937	1,956	2,308
Emergency medical technicians	12,757	17,873	16,028
EMT-Intermediates	212	539	1,157
EMT-Paramedics	37	159	469
Mobile intensive care nurses	13	319	326
Totals	14,956	20,846	20,288

North Carolina has two categories of ambulance personnel beyond the basic EMT — the EMT-intermediate and the EMT-paramedic — both of which are certified by the Board of Medical Examiners. Presently, there are 1,157 certified EMT-intermediates and 469 certified EMT-paramedics in the state. Most training at these levels takes place through local hospitals which serve as sponsors for advanced life support programs. However, five community colleges have established two-year associate degree programs in emergency medical science. Persons graduating from these programs not only have the clinical training and skills qualifying them for certification as EMT-paramedics, but they have had course work in business, psychology, and other areas to enhance their upward mobility in the system. Graduates of these programs serve as an important manpower pool for EMS services statewide, particularly those at the advanced life support levels.

Recognizing the need to train today's EMS managers, the EMS Management Institute was established in 1982 at the University of North Carolina at Charlotte. This is an intense continuing education program conducted over a nine-month period aimed at upgrading the management skills of the practicing EMS manager. Some 40 persons have now successfully completed this program.

Training programs have also been established for hospital emergency department personnel. Under a grant from the Department of Health, Education and Welfare, the Office of Emergency Medical Services established the Emergency Nurse Education Program with the purpose of upgrading the skills and knowledge of the ED nurse. Before funding expired in 1982, over 290 nurses went through this course. The program was subsequently reformatted into modules and can be offered as a continuing education program by an area health education center or an individual hospital. Also, 326 nurses are approved by the Board of Medical Examiners as mobile intensive care nurses, au-

thorizing them to give orders over the radio to EMT-intermediates and EMT-paramedics in the field.

Another significant achievement in the area of training is the establishment of residency programs in emergency medicine at Bowman Gray School of Medicine, Charlotte Memorial Hospital, and East Carolina School of Medicine. Together they have 36 emergency medicine resident positions which serve as an important source of physicians for staffing hospital emergency departments in the state. Emergency medicine was approved as a medical specialty in 1979 bringing new standards of training and expertise to physician staffing of the emergency department.

Hospitals and Medical Control

Hospital emergency services have also undergone a major transformation during the past decade. The emergency room has given way to the emergency department, symbolizing a much more organized and committed approach to treating the emergency patient on the part of an institution. This is further evidenced by the change in physician staffing patterns in the emergency department. In 1973 only 21 hospitals in North Carolina had 24-hour physician coverage in the emergency department. This has since risen to 76 or 63 percent of all hospitals in the state providing emergency services. An even greater number have coverage for one or two shifts each day and on the weekend. Tables 3 and 4 show the number of hospitals with 24-hour physician staffing in the ED by hospital bed size and number of ED visits annually. The Program on Access to Health Care played an influential role in this area by contributing over $3.2 million to 54 hospitals to assist them in establishing 24-hour coverage in the ED. The end result has been increased availability of medical care for the citizens of North Carolina, especially the critically ill and injured.

A less tangible, but equally important, change has been the increased involvement of the hospital and its medical staff in the overall emergency medical services system. An objective of the state EMS program has been to break down the barrier that has traditionally existed between the prehospital provider and the hospital ED to enhance the continuity of care from the scene to the emergency department. Advanced life support programs are considered an extension of the services of the hospital emergency department to the site of the accident or illness and, thus, regulations promulgated by the Board of Medical Examiners require that such programs be sponsored by a hospital, rather than by an individual ambulance provider. Currently 58 of the 120 hospitals offering emergency services serve as sponsor hospitals for advanced life support programs. Additionally, nine have been designed as resource hospitals with responsibilities for coordinating and standardizing ALS programs on a regional basis and for providing back-up physician support for field technicians associated with other sponsor hospitals. The strong medical orientation of these programs is further demonstrated by the requirement that each have a designated medical director.

Table 3

Hospitals with 24 Hour ED Physician Coverage by Bed Size — 1983

No. Beds in Hospital	No. of Hospitals	No. with 24 hr ED Coverage	Percent with 24 hr ED Coverage
0-50	13	0	0
51-100	30	9	30
101-150	25	19	76
151-200	17	15	88
201-250	3	3	100
251-300	7	6	86
301-350	6	6	100
351-400	3	2	67
401 & over	16	16	100
Totals	120	76	63

Table 4

Hospitals with 24 Hour ED Physician Coverage by Number of ED Visits — 1983

No. of ED Visits	No. of Hospitals	No. with 24 hr ED Coverage	Percent with 24 hr ED Coverage
1-1,000	3	1	33
1,001-3,000	7	0	—
3,001-5,000	9	1	11
5,001-10,000	27	8	30
10,001-15,000	22	15	68
15,001-20,000	16	15	94
20,001-30,000	19	19	100
30,001-40,000	9	9	100
40,001-50,000	5	5	100
50,001-60,000	2	2	100
60,001 and over	1	1	100
Totals	120	76	

One of the mandates given to the Department of Human Resources by the EMS legislation was the development of comprehensive emergency treatment centers. In this regard, the Office of Emergency Medical Services' attention has been largely directed to establishing a trauma system with designated centers for treating the most severe cases. Published studies show that reductions in morbidity and mortality can be achieved by concentrating the treatment and care of the severely traumatized patient in facilities specially equipped and staffed to handle them.[1, 2] To date, the Secretary has designated three statewide or Level I trauma centers — Duke University Medical Center, N.C. Baptist Hospital, and N.C. Memorial Hospital — and one regional or Level II trauma center, Pitt County Memorial Hospital. Such a designation recognizes the commitment of the institution to the treatment of the trauma victim and its willingness to meet criteria adopted by the State from that set forth by the American College of Surgeons. Efforts are ongoing to identify and designate regional trauma centers in other parts of the state.

In 1983 monies were appropriated by the General Assembly to establish a state poison control and information center. The Department of Human Resources entered into a contract with Duke University Medical Center to expand their existing services in this area to include a toll-free telephone line manned by trained poison information specialists 24 hours/day. A survey conducted by the Office of Emergency Medical Services in 1981 revealed 11 hospitals providing some type of poison information ser-

vice to the general public, but with the exception of Duke, all served a smaller geographical area. Future activities will focus on tying the state center and the regional/local centers together into an effective network.

Finally, in the area of hospitals, all of those providing emergency services have been categorized according to their ability to treat emergent patients in eight critical care areas — trauma; burn; spinal cord; cardiac; behavioral; poisoning/drug; neonatal, perinatal and pediatric; and acute medical. Hospitals are categorized as a Level I, II, or III (I denotes greatest capability) in each area according to criteria set by the State through the State EMS Advisory Council. Those not meeting at least the Level III criteria for an area are not categorized.

Medical control is an important principle in the modern day emergency medical services system and one that is increasingly recognized as essential to the delivery of quality emergency medical care. In essence, medical control refers to the management and accountability for the medical care aspects of the EMS system — a direct recognition of the fact that EMS is medical in nature. It includes oversight of the training of the prehospital personnel, the development of treatment protocols for use by the prehospital technicians in rendering medical care in the field, and evaluation of the medical care provided by the system.[3]

Structurally, the concept of medical control begins with the medical director of the Office of Emergency Medical Services, who oversees the medical aspects of the state program, and continues throughout the entire EMS system. Each regional EMS council has a part-time medical director with responsibilities at the regional program level which include the development of region-wide treatment protocols for prehospital personnel, establishment of transfer agreements, categorization of hospital emergency services, and consultation on the medical content of training programs.

At the local level, medical control activities are much more operationally oriented. They involve giving orders to field technicians over the radio, evaluating the quality of prehospital emergency care, and assessing the capabilities of field technicians in addition to planning and administrative responsibilities similar to those of the regional medical director. A recent statewide survey showed that 151 ambulance providers claim to have a medical director. Unfortunately, their involvement in medical control activities is often very little. Advanced life support programs are required by regulation to have a system of medical control including a designated medical director. There is no such requirement for those functioning at the basic level, and those in ALS programs account for about one-half of the 151 who have a medical director. The lack of medical direction and medical control at the basic level is a shortcoming that needs to be addressed.

Transportation

A 1965 study of ambulance services in North Carolina reported that only 18 percent of the 905 ambulances in the state were straight ambulances while 54 percent were combination hearse and ambulance.[4] A subsequent survey by the Research Triangle Institute in 1972 found that only 311 of 776 ambulances could be considered suitable for EMS on the basis of vehicle age, type, equipment, etc.[5] Today the ambulance remains the single most visible symbol of emergency medical service, but the hearse and station wagon have given way to a vehicle that is better designed and equipped.

Surprisingly, the actual number of ambulances has not increased substantially relative to the extent of other improvements in EMS. In 1984, there are 1,164 ambulances permitted by the Office of Emergency Medical Services signifying compliance with minimum staffing and equipment standards set by the Medical Care Commission. Most are Category I ambulances, equipped and staffed to transport emergency cases, although legally they are authorized to carry non-emergency patients. State regulations were amended in 1983 to establish a Category II ambulance which is permitted solely to transport non-emergency cases between a residence and a medical facility or between two medical facilities. Because of the limitations of this type of vehicle, very few are in operation; however, their utilization is expected to increase in the years ahead.

Approximately 75 percent of the 1,164 vehicles meet the more exacting requirements of the Federal Ambulance Specification, which calls for 60 inches of headroom in the patient compartment versus a minimum state requirement of 52 inches. Recitation of the specific design and equipment requirements for ambulances would serve little useful purpose. The significant aspect of such changes is that ambulances are now designed with sufficient room for the patient and for two or more technicians to administer care while en route, as well as for the necessary rescue and medical equipment. Again, the patient and the delivery of emergency medical care are the focal points.

Ambulance coverage is provided to all parts of the state by the 514 ambulance services in the state, each of which operates 1 or more of the 1,164 permitted ambulances. Response time, the time from the receipt of the call for assistance to arrival at the scene, varies from community to community, but all counties report average response times within the state established minimums of 10 minutes in an urban area and 30 minutes in a rural area. Statewide, the average response time for emergency calls is 8.7 minutes. Of the 100 counties in the state, 66 report an average response time of 10 minutes or less; 32 of between 11 and 15 minutes; and only 2 over 15 (16 minutes). A recent survey conducted by the Office of Emergency Medical Services of all ambulance providers in the state showed that there was a total of 449,803 runs in 1983 (based on the fiscal year of the provider). Emergency runs comprised 55.9 percent of the runs and non-emergency 31.0 percent. Search and rescue, standby, and other miscellaneously classified calls made up the balance.

Tiered response systems have been established in some counties where first responder organizations have been formed for the purpose of further reducing the response time. First responders are organizations or agencies, most commonly fire departments, police departments, or non-transporting rescue squads, with personnel trained in basic emergency medical care who are dispatched to the scene to provide immediate care to the victim until the ambulance crew arrives. There are 130 such organizations in North Carolina functioning in 26 counties.

The MAST (Military Assistance to Safety and Traffic) Program operated by the 57th Medical Detachment out of Fort Bragg provides the state's only helicopter emergency medical evacuation service. Several hospitals have stated an interest in establishing a hospital-based helicopter program. Given the recent interest, the entire area of emergency air evacuation is being studied by the Department of Human Resources to ascertain the approach that might best serve the citizens of North Carolina.

Communications

Communications is often said to be the thread that ties the various elements of the EMS system together. If this is the case, there was certainly very little holding North Carolina's EMS system together prior to the early 1970s. Public access to prehospital emergency medical care was difficult and complicated by the variety of telephone numbers to be called within a county to request an ambulance. Dispatch was often slow and uncoordinated. Even if the ambulance and the hospital both had two-way radios, they were more likely than not to be on different frequencies so that the ambulance personnel and hospital ED staff could not communicate with each other. Often ambulances within the same service had different radio frequencies and coordination with other public safety agencies was practically nonexistent.

A simplified means of access to prehospital emergency care continues to be a goal of the state EMS program. Only 10 counties have implemented 911 systems countywide for use in obtaining police, fire, and emergency medical assistance. This remains the ultimate target, but progress is slow for many reasons including turf and political squabbles among local public safety agencies, costs, and the multiplicity of phone companies across the state. Another 54 counties have at least a single seven-digit number countywide for calling for an ambulance, the minimum deemed acceptable by the Office of Emergency Medical Services. While considerable progress has been made, multiple telephone numbers, which can cause unnecessary confusion and delay, still exist in 36 counties. Coordinated dispatch through a single central point is possible in 63 counties.

Ambulance and ambulance to hospital communications have improved significantly, particularly in terms of coordination and standardization among local jurisdictions. All of the 120 hospitals providing 24-hour emergency service have two-way radios and the capability to transmit and receive on the VHF (very high frequency) frequencies of 155.280 MHz and 155.340 MHz. Among the State's ambulances, 97 percent have operational two-way radios equipped to operate on the standard VHF frequencies, enabling the field technicians to talk directly with a physician or nurse in the hospital emergency department.

Having achieved statewide standardization for the most part, the VHF spectrum serves as the basic communications system for EMS, although the limited frequencies available pose some crowding problems. In 1973 the Federal Communications Commission allocated 10 frequency pairs on the UHF (ultra high frequency) spectrum for medical communications and authorized their use for the transmission of biomedical telemetry, an essential part of an EMT-paramedic service. Cost, as well as a lack of an immediate need, caused the Office of Emergency Medical Services to decide to implement UHF EMS communications systems on a county by county basis, rather than attempting to move immediately statewide. Priority has been given to those counties that have an EMT-paramedic program or are planning to initiate one and, thus, have a need for biomedical telemetry. Presently, 30 counties have complete UHF EMS communications systems. These are supported by a network of 14 areawide radio repeater sites operated and maintained by the Office of Emergency Medical Services which facilitate inter-county and regional EMS communications.

The Future

The general public has come to appreciate and recognize the value of a good emergency medical services system. Consequently, their expectations are much greater today than they were 10 years ago — and they should be. Paramount among the issues facing EMS in the future is the quality of the medical care rendered to the critically ill and injured. Efforts so far have focused on system development, yet the establishment of a system brings with it the responsibility to maintain and improve upon the level and quality of the service. Attention must be directed to building quality assurance procedures and protocols into the system at various points, just as hospitals and their medical staffs have had to do. Additionally, research in emergency medicine and evaluation of the delivery system will play a greater role in tomorrow's EMS system than it has in the past. The EMS system will have to maintain its flexibility to adjust to new and more effective treatment modalities and service delivery methods and incorporate them into ongoing operations.

Although there have been many improvements in the delivery of emergency medical care, North Carolina's EMS system is far from complete. However, a solid foundation has been laid and the basic framework established for the continued development of the system.

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SCIENTIFIC ARTICLE

A Philosophy for the Care of Trauma Patients With Multiple Musculoskeletal Injuries

Laurence E. Dahners, M.D.

• *A primer on the care of the patient with musculoskeletal injuries, from the acute period to rehabilitation.*

Introduction

IN this day of high speed motor vehicle accidents, multiple injuries in a single patient are a frequent problem. Largely because of the efforts of the American College of Surgeons Advanced Trauma and Life Support Courses (ATLS) our ability to transport, resuscitate and stabilize these patients has improved and more patients are surviving the acute injury to require more definitive treatment. This means that the physician is sometimes called upon to address the patient with multiple extremity injuries and must decide when, how and in what order to treat these injuries.

The purpose of this paper is to discuss where, in the general priority of things, the locomotor injuries should be addressed and the order in which they should be treated. In addition, there is some discussion of how the treatment of a particular fracture, in the setting of multiple fractures, differs from the care of the single fracture alone.

Where Musculoskeletal Injuries Fall in the General Scheme of Trauma Care

It is useful to divide the care of the polytrauma patient into five stages: acute, primary, secondary, tertiary and rehabilitative. In the first or acute stage immediate life threatening injuries such as pneumothorax, massive bleeding or intracranial hemorrhage should be treated and musculoskeletal injuries usually can be ignored. In the primary phase visceral injuries such as bowel rupture and limb threatening injuries such as vascular disruptions, compartment syndromes, open fractures and open joints are treated. In addition, it is probably important to operatively stabilize major long bone fractures during this period if feasible. During the secondary period attention is turned to sustaining the vital organs through a post-traumatic illness characterized by catabolism and pulmonary dysfunction. In the tertiary period complex joint fractures are reduced and fixed, ligaments are repaired, and wounds are covered. Finally, in the rehabilitative period reconstructive operations such as bone grafts and arthroplastic procedures are carried out.

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Acute Period (Lifesaving)

The acute period is a time of resuscitation from life-threatening injuries to the heart, lungs or central nervous system. The management of the patient during the acute period is well addressed by the ATLS course and physicians involved in the care of trauma patients should strongly consider taking the course.

During this period it may be necessary to address one orthopedic injury and that is the unstable pelvic fracture. These fractures involve the major ring of the pelvis and are displaced more than one centimeter. They are often responsible for life-threatening hemorrhage and, while the first line of defense is fluid replacement and tamponade with MAST trousers, sometimes early external fixation may be life saving. Placing three to six percutaneous pins in each iliac wing and connecting them with an external frame stabilizes the pelvis, thus preventing the constant disturbance of clots formed on the rapidly bleeding cancellous bone bed. In general this form of stabilization provides more reliable control of hemorrhage (>90% in one series) than radiographic arterial embolization (10%).

The acute period should last only one to two hours and there are only two other orthopedic injuries which should be considered during this period. These are dislocations of the knee and subtalar joint, which often obstruct the adjacent vessels (the popliteal and posterior tibial, respectively). Often they are very easily reduced by increasing the deformity, applying hand traction, and easing the limb back into a normal position. Fifteen seconds spent thus may save a limb without undue risk to life. Of course the first priority should be oxygenation and circulation to the vital organs and repeated attempts at reduction cannot be justified.

Primary Period (Limbsaving)

The primary period is that first, "golden," twelve hours after injury while the patient is in relatively good condition. Post-traumatic respiratory distress has not set in as yet, the wounds have not become soupy and secondarily infected and the patient will probably tolerate surgery better than he will anytime in the next several days or weeks. It may be a serious mistake to put off a procedure "until he's in a little better shape," especially when some of those procedures may shorten the course of his post traumatic illness.

During the primary care period transfer to a tertiary care center should be considered if the multiplicity of injuries warrants it, the distance is not too great, and the patient seems stable enough to tolerate the transfer. The problems which must be addressed during the primary period are those which will present a significant threat to life or limb if not treated within six to twelve hours. Included are such non-locomotor injuries as peritoneal soiling from rupture of the hollow organs.

In the care of the locomotor system the first priority is to restore perfusion. Vascular repair should be carried out and limbs displaying signs of a compartment syndrome should have fasciotomy. A dislocated knee or subtalar joint must be reduced by now and in addition dislocations of the hip (which compromise the blood supply to the femoral head) should be reduced. If perfusion of muscular tissue is not restored within six hours the success rate falls off dramatically. Time should not be lost in the radiology suite obtaining definitive angiography; rather a single shot arteriogram of the injured area should be obtained in the operating room (this is almost always adequate).

The next priority is the debridement and irrigation of open fractures and in the multiply injured patient strong consideration should be given to operative stabilization of open fractures of the femur and tibia. This operative stabilization is usually achieved by external fixation, but occasionally internal fixation is appropriate. While external fixation is without a doubt the safest means, internal fixation should be considered for fractures which are relatively clean, for those in which the approach for internal fixation has already been made by the traumatic injury, and for displaced articular fractures.

Major trauma centers have recently produced evidence that rigid operative stabilization of major long bone fractures (especially the femur) during the primary period decreases the severity of the post traumatic respiratory distress syndrome. Therefore, strong consideration should be given to intramedullary nailing of femur fractures, by closed techniques if possible, but by open technique if necessary. Many would advocate nailing of grade one open (small, clean, open wound produced by the bone puncturing the skin from the inside out) femur fractures as well. Some would even advocate extending the indications for intramedullary nailing, in the multiple trauma patient, to include those outside the middle third and those with comminution. Another solution is a simple, single bar, lateral, external fixator (such as the Wagner leg lengthening device), which connects pins in the greater trochanter to pins in the supracondylar region. This acts as a "mobile traction unit" allowing early mobilization of the patient out of the supine position for better pulmonary toilet.

Secondary Period (Fine Tuning of the Vital Organs)

During this period the major objective is to sustain the patient through a frequently severe post-traumatic illness, characterized by respiratory insufficiency and a catabolic state. Ventilatory support and alimentation (by feeding tube if possible or by venous routes if necessary) are the keystones of treatment. Providing optimal care (such as early alimentation) is very important to the effort of keeping this period as short as possible (preferably under one week) because many of the complex surgical procedures of the tertiary period are very difficult two weeks after injury.

During this period further insult to the system, in the form of surgical procedures, should be avoided if possible. It is of great importance to eliminate septic foci which will prolong or increase the illness. Transcutaneous lines should be changed and wound dressings closely observed. Infected wounds must be drained and debrided, and occasionally something as drastic as an amputation may be necessary to eliminate a source of sepsis.

Tertiary Period (Fine Tuning of the Locomotor System)

When the patient's respiratory status has improved and he has become anabolic, further surgical treatment of the locomotor system is appropriate. Ligamentous repairs, as well as reduction and fixation of upper extremity fractures and closed articular fractures should be undertaken during this time. Wounds are closed or skin grafted and flaps may be swung during this period if necessary. Spine fractures are usually stabilized by operative means during the tertiary period, though very unstable fractures with neurologic sparing may need to be done during the primary period to allow mobilization of the patient (for pulmonary toilet) without risk of further neurologic injury.

When the illness of the secondary period lasts more than one to two weeks the physician is often faced with a difficult choice. He may operate while a good reduction or repair is still possible (within one to two weeks of injury) but incur risks of anesthetic complication and wound infection. On the other hand, he may wait to operate until the risk is less but will be forced to accept less than optimal locomotor results in the long run.

Rehabilitative Period

The rehabilitative period falls after all surgical repairs are completed. It is a time during which the patient is mobilized by physical therapy, the fractures heal and the patient is restored to the best obtainable locomotor status. This period may last for the remainder of the patient's life and through many reconstructive procedures.

Bone grafts to stimulate healing of delayed or nonunions of fractures are certainly appropriate. Malunions of fractures not treated satisfactorily because of intervening factors may need to be taken down and reduced. Ligament reconstructions for unstable joints and muscle transfers for motor deficits may be needed. Joint arthroplasty or arthrodesis may be necessary for joints which could not be adequately repaired during the tertiary period.

Operative Versus Nonoperative Treatment in the Multiply Injured Patient

There is accumulating evidence in favor of taking a more aggressive operative approach to multiple fractures. This has been shown to be important in the treatment of femoral fractures because of the improved pulmonary toilet that early mobilization allows. Some trauma surgeons go so far as to liken traction to crucifixion of the multiply injured patient. They feel that the supine position results in ventilation/perfusion mismatch, pneumonia, deep venous thrombosis, pulmonary embolism and decubiti.

Multiple fractures often respond poorly to nonoperative treatment because optimal conservative treatment of one fracture compromises the treatment of other fractures. This is especially true of multiple fractures in the same limb where the optimal position for reduction of one fracture may prevent reduction of another. Ipsilateral femur and tibia fractures have a high incidence of malunion and nonunion unless treated operatively. Gravity is often an important factor in the reduction of a humerus fracture and in the supine patient with a femur in traction it may be very difficult to maintain adequate humeral fracture reduction. It may be wise to internally fix the femur so that the patient may be maintained in an upright position for nonoperative treatment of the humerus.

Many of the fractures in the multiple trauma victim will be open because of the high energy of the accident. For many physicians this raises the dilemma of how to stabilize the fracture for the best care of the soft tissues and mobilization of the patient. An external fixator is the safest means for this, providing rigid immobilization of the fracture, without extensive surgical dissection for device application as with internal plates. In addition to providing better immobilization of the fracture (and thus protection of wounded tissues) without immobilization of the adjacent joints, it also allows better wound care (access) than a cast. In some cases an extensive wound allows application of internal fixation devices without further dissection (and thus injury to the blood supply) and in this instance internal fixation is probably justified. Suboptimal internal fixation devices (short plates or circlage wires alone) are not justified as they will usually fail, leaving you with the worst of both worlds (an unstable fracture with a foreign body).

Open, displaced, articular fractures should usually be treated with internal fixation as it provides the only means for maintenance of a perfect reduction. A windowed cast is seldom capable of maintaining reduction. It serves little purpose to ensure post-traumatic arthrosis secondary to malreduction of articular surfaces because of a fear of post-infectious arthrosis. There is experimental as well as clinical evidence now that fractures immobilized by internal fixation do as well in the face of infectious organisms as those treated without implants. Internally fixed fractures have a lower incidence of malreduction, and if they become infected, the infection does not seem to be as severe as in fractures healing with large quantities of callus (as in a cast).

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Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation, see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

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SCIENTIFIC ARTICLE

New Principles of Resuscitation for Brain and Spinal Injury

Michael J. Rosner, M.D., Zev Elias, M.D. and Irene Coley, P.A.-C.

• *Current do's and don't's in the early care of patients whose injuries affect the brain and/or spinal cord.*

THE resuscitation and care of the brain injured patient begins with a clear statement of the neurologic condition of that patient. This is important for purposes of communication with referral centers as well as to clarify issues for the treating physician. Such terms as "stuporous," "obtunded," and "altered mental status" have little intrinsic meaning and vary widely in the manner in which they are used; in recent years they have been replaced by the Glasgow Coma Scale (GCS), table 1. Particularly for the purposes of communication, the Glascow Coma Scale has shown itself to be extremely objective and easily learned, and provides a uniform terminology for communication with other physicians.

The core of the Glascow Coma Scale is its treatment of the neurologic exam as a stimulus response arrangement with either voice or painful stimuli producing a verbal or motor response. Thus, patients either open their eyes spontaneously, or to voice, or to pain, or not at all, and such terms as stuporous and lethargic are never required. Similar scales are used for assessing verbal and motor responses. The Glascow scale is also easily adapted to intensive care or recovery room flow sheets.

Depression in the level of consciousness, or lack of eye opening to voice or pain, implies a very few reasonably specific alterations in either the anatomic or physiologic status of the patient. For consciousness to be intact, the reticular activating system in the deep medial structures of the brain stem must be intact. Small lesions in this system and somewhat higher up in the diencephalon are able to produce impairment in the level of consciousness. Depression in the level of consciousness may also be brought about when very large areas of the hemisphere are affected by a lesion, even though the brainstem may be intact. The implication is that lesions that affect only relatively small areas of the hemisphere do not produce significant depression in the level of consciousness. This is typical of the vast majority of hemispheric infarcts or strokes, small intracerebral hematomas, and many small traumatic contusions. Lesions that affect the hemispheres diffusely, such as anoxia, ischemia, and metabolic poisons such as barbiturates, are capable of depressing the level of consciousness without first affecting the brainstem. Many penetrating cerebral wounds, such as stab wounds of the cranium or low velocity bullet wounds such as inflicted by a .22 caliber short pistol, may actually affect only a small volume of hemispheric tissue and these patients may well present to the emergency room spontaneously opening their eyes, speaking, and following commands.

TABLE 1
Glasgow Coma Scale

Eye Opening	
Spontaneous	4
To verbal command	3
To pain	2
None	1
Vocal Response	
Oriented/conversant	5
Disoriented	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Motor Response	
Obeys commands	6
Localizes pain	5
Flexion-withdrawal	4
Flexion-abnormal	3
Extension	2
None	1

The pupillary light response and extraocular motility provide assessments of brainstem function in addition to level of consciousness and these are worth a very brief review. Pupillary constriction is a function of the intact 3rd nerve which has its nucleus ipsilaterally near the top of the brainstem (mesencephalon). A light stimulus applied to the eye causes reflex constriction of the pupil by more or less direct connections from the lateral geniculate body to the 3rd nerve nuclei. The 3rd nerve and its nuclei are responsible for medial, superior and inferior movement of the eye, as well as pupillary constriction. The 6th nerve moves the eye laterally via the lateral rectus muscle and has its nucleus on the ipsilateral side of the pons, which is just about an inch and a half below the 3rd nerve nucleus. The 3rd and 6th nerve nuclei are connected by means of the medial

From the Trauma Service, Section of Neurosurgery, Department of Surgery, University of North Carolina — North Carolina Memorial Hospital Statewide Trauma Center, Chapel Hill 27514.

longitudinal fasciculus (MLF), which also connects to the corresponding contralateral structures. Thus, when gaze is directed to the left, the left lateral rectus contracts, the right medial rectus contracts and the antagonist muscles relax, all coordinated by the MLF. In patients with severe abnormalities in the level of consciousness, passive movement of the head from side to side will leave the eyes moving together as if they were staring at a fixed point in space. This is known as the oculocephalic reflex or the "dolls eyes" maneuver. Thus, intact "dolls eyes" to examination in the patient with a depressed level of consciousness implies that the segment of brainstem from the pons to the mesencephalon is more or less intact.

Decortication and decerebration are both terms which have been replaced on the Glascow coma scale by "abnormal flexion" and "abnormal extension." A more general term for these abnormal movements is "posturing." Abnormal flexion implies loss of inhibitory input upon the red nucleus and, therefore, unimpeded activity of the rubrospinal tract (increasing flexor tone). "Abnormal extension" is similar in that it occurs when inhibition from supranuclear structures upon the vestibular nuclei in the pons is lost and the vestibulospinal tract is unhampered; extensor tone and movements are facilitated. Any lesion capable of impairing the supranuclear inhibition of these structures is thus capable of producing decortication or decerebration and the presence of these movements is specific for where a lesion is *not* as opposed to where it specifically *is*. Very large hemispheric lesions such as anoxia, or large ischemic infarcts, are able to produce this loss of inhibition just as precisely placed, smaller lesions, limited to inhibitory tracts, may produce such behaviors.

When the pupillary light reflex and extraocular motility are intact in a patient exhibiting posturing-type movements, then the neurologic condition is usually metabolic in origin and not related to a mass lesion. This is because the areas that subserve these abnormal motor movements are very closely related to those that subserve the pupillary and extraocular motor function. If the latter are intact, then the implication is that a *mass* lesion is not causing the dysfunction.[6]

An emerging concept in the care of brain injured persons is the cerebral perfusion pressure (CPP). This is defined as the difference between the systemic arterial blood pressure and the intracranial pressure. Normally, the cerebral perfusion pressure is between 80 and 100 mm Hg. It can be adversely affected by increases in the intracranial pressure or decreases in the systemic arterial pressure. The immediate implication is that if a patient with an intracranial mass lesion (high ICP) presents in shock (low SABP), then his cerebral perfusion pressure is probably very low indeed. Cerebral blood flow, even in the face of autoregulation, is dependent upon CPP and falls off rapidly when cerebral perfusion pressure drops below 60 mm Hg; this can cause ischemic damage superimposed on the mechanical effects of the injury (figure 1).

Hypoxemia is a very powerful cerebral vasodilator, as is hypercarbia. Therefore, the effects of hypoxemia, in addition to potential hypoxic damage, include increasing the intracranial pressure because of the increase in cerebral blood volume which occurs as the result of vasodilatation. Hypercarbia acts in a similar manner. Both can lead to severe impairment of the CPP.

By applying these simple physiologic principles, it is immediately apparent that shock in the face of a cerebral mass lesion in a patient who is hypoxic and potentially retaining CO_2 produces an absolutely devastating scenario in which the cerebral perfusion pressure is successively lowered by each of these factors. It is no surprise that many fatal cerebral injuries are accompanied by pathologic evidence of ischemic infarction and anoxic cell change.

Any patient suspected of having a brain injury should immediately undergo fluid resuscitation in an effort to normalize his systemic arterial blood pressure. Immediate knowledge of the intracranial pressure in the emergency room is usually not available, but treating the patient *as if* his intracranial pressure is elevated in the face of a low blood pressure is a very practical approach. Similarly, the use of intubation and mechanical ventilation in any patient who even appears to have marginal respirations or thoracic injury would help to avoid or ameliorate the effects of hypoxemia and hypercarbia.

It is obvious that one does not intubate patients who have had only transient loss of consciousness, and this form of therapy as a routine for brain injury should be reserved for

1. patients who have obvious chest injuries such that hypoxemia is likely to occur;
2. patients whose motor response to painful stimulus is no better than normal flexion or withdrawal;
3. patients who are unable to follow commands.

Using the latter criterion alone, for every 100 patients *unable to follow commands* when admitted to the emergency room, thirty to forty will die or remain in a persistent vegetative state. Fifty to sixty will make a good to moderately good recovery, and approximately 10% will be severely disabled.[2, 5] Only a few patients will be unable to follow commands because of the temporary effects of drugs, alcohol, or less severe transient injuries. So this patient, who is unable to obey commands, must be viewed as having suffered a major brain injury *until proven* otherwise.

The key to optimizing recovery from brain injury is early and immediate removal of a mass lesion in those patients harboring one (40% of those who cannot follow commands when first admitted to the emergency room). The remainder of the treatment of these patients is avoiding a secondary insult such as anemia, hypoxemia, and hypotension. It follows that these maneuvers and a definitive neurosurgical evaluation must occur very quickly to optimize results. Currently the most effective and fastest technique for the evaluation of the presence of a mass lesion is the CT scan. If an obviously, and severely, brain injured patient arrives at an emergency room without CT scan facilities, arrangements ought to be made immediately for his transfer after restoration of blood volume and oxygenation. If these facilities are locally available, they should be used.

Mannitol is an osmotically active agent which decreases the viscosity of the blood, improves red cell deformability, and thereby enhances cerebral blood flow and oxygen delivery. Because blood flow and oxygen delivery have been improved by this agent, vasoconstriction is able to occur

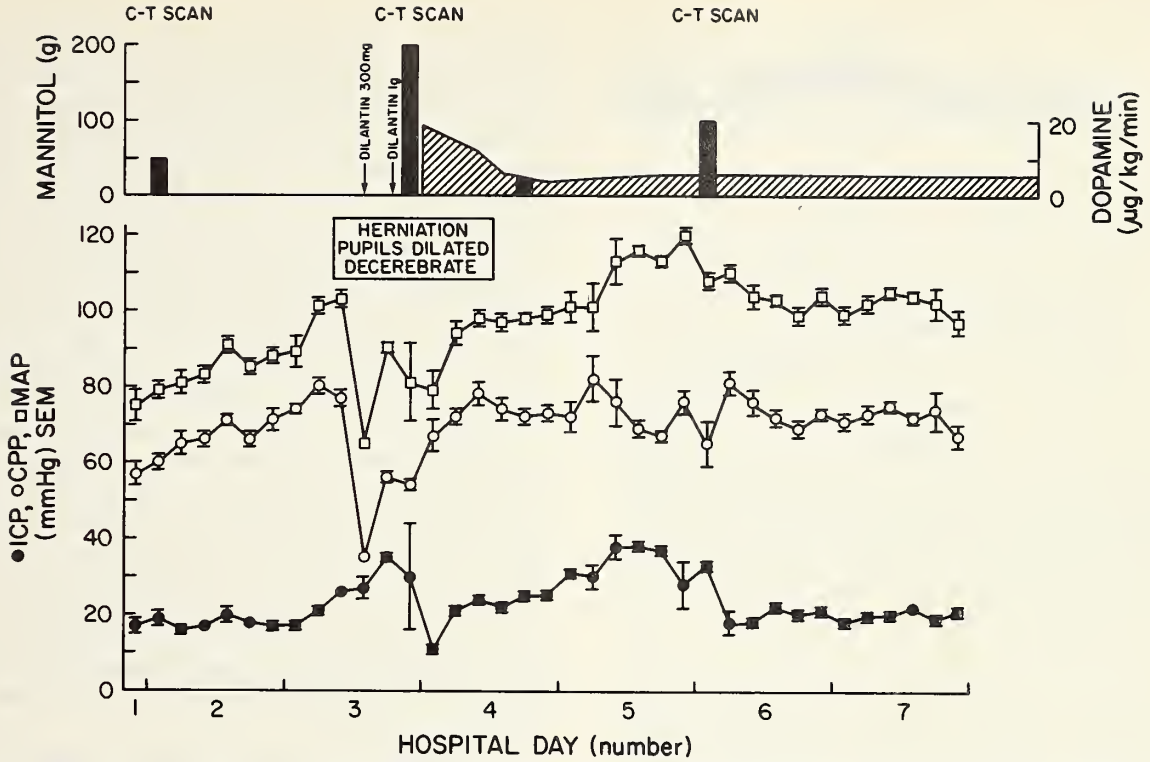


Figure 1. *This graph depicts the systemic arterial pressure (MAP), cerebral perfusion pressure (CPP), and intracranial pressure (ICP) over the first week in a patient who has just had an acute right subdural hematoma removed. For the first 48 hours, the ICP generally remained low (<20 mm Hg) but was accompanied by increasing systemic pressure. The patient remained neurologically stable, which involved opening his eyes to command, localizing a stimulus on the right and demonstrating a withdrawal response on the left. By the third day, he had a very slowly rising intracranial pressure and at approximately 4 a.m. he had a seizure. During the time of his seizure, his intracranial pressure went up substantially but because there was no perfusion pressure decrement he did not change neurologically. However, when 300 mg of Dilantin were given intravenously and followed by an additional 1000 mg, his systemic blood pressure dropped substantially, his perfusion pressure dropped to below 40, and his intracranial pressure rose very substantially. Both pupils became fixed and dilated and he became bilaterally decerebrate. Mannitol was given and a CT scan obtained which was basically unchanged from early after surgery. He was returned to the intensive care unit where he was placed on a dopamine drip in order to stabilize and elevate his systemic pressure to approximately 100 mm Hg and maintain his CPP at 70 or better. Only two additional doses of Mannitol were required and his ICP gradually stabilized. On the fifth day, an intracranial pressure spike occurred which was related to a drop in systemic pressure (not apparent on this graph). Mannitol was given and dopamine was continued. The patient did not change neurologically throughout this period and a CT scan was unchanged. The patient throughout improved and by the 7th day was opening his eyes to command, localizing painful stimuli with the right side and withdrawing on the left. Within the next few days, he was following verbal commands and using both sides purposefully. A mild hemiparesis was present at the time of his transfer. (Blood pressure, CPP, and ICP are plotted as the mean plus or minus SEM of 4 hourly observations; thus important transients which occurred with this patient are not necessarily obvious from this form of plot.)*

and cerebral blood volume is diminished. Mannitol may also have a dehydrating effect on the brain, though in recent years this has become controversial and, in fact, no direct evidence exists for mannitol being effective in removing edema or excess water from the brain.[6] However, it is extremely effective at stabilizing and at least temporarily reversing neurologic deterioration when it is due to a cerebral mass lesion.

If mannitol is to be used, it must be with the recognition that a massive diuresis will quickly occur and that a urinary catheter is necessary. After a single bottle of 20% mannitol (500 cc: 100 grams), the average adult will excrete between 1000 and 2000 ml urine. If this volume is not replaced, hypotension can be potentiated or precipitated, and the low perfusion pressure may *increase* ICP. Contrariwise, immediately after infusing a large bolus of mannitol extravascular water is drawn into the vascular space and immediate and effective volume expansion occurs. The blood pressure rises, tissue perfusion improves and ICP comes down (figure 2). However, this is transient because of the inevitable diuresis. Thus, mannitol is *not* contraindicated in the face of hypotension, but it *must* be accompanied by adequate fluid resuscitation.

Mannitol should be used immediately in any patient showing signs of progressive neurologic deficit, and in particular those with limb paresis and pupillary abnormalities. Given adequate fluid resuscitation and observation, it may be used as an agent to "buy time" while a patient is sent to CT scan. In days prior to CT scan, many neurosurgeons asked that mannitol not be given because it could

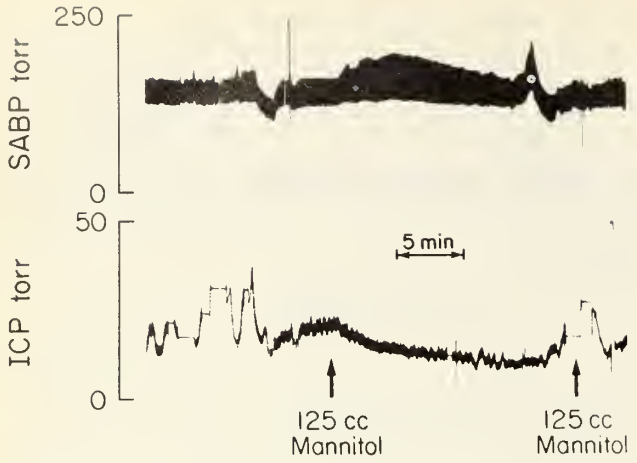


Figure 2. *This trace is from another brain injured individual and shows the effect of an infusion of a small dose of Mannitol upon both the ICP and blood pressure (SABP). Systemic pressure is elevated, intracranial pressure is reduced. This reflects both the improvement in perfusion pressure and the rheological effects of Mannitol which improve oxygen delivery to tissues.*

give a false sense of security when evaluating a newly arrived patient. However, with the advent of widespread CT availability, following patients "clinically" for deterioration is virtually useless. It is generally recommended that we identify those with a mass lesion *before* they dilate a pupil and herniate, and if mannitol can provide a time "buffer," then this is clearly worth any temporary uncertainty about specific neurologic findings or questions of progressive neurologic deficit. If in doubt, use mannitol, but replace the fluid lost!

The use of steroids in brain injury is modestly controversial. There have been two relatively recent prospective, double-blind studies using no steroids, low dose dexamethasone and high dose dexamethasone. Neither study succeeded in showing any improvement in either mortality or morbidity in the long or short term in either low or high dose steroid treated groups when compared with placebo (saline) treated controls.[1, 4] The complications of steroids also seem to be relatively minor, with only one study demonstrating an increase in pneumonitis in the high dose, steroid treated, brain injured group. A potential complication is the newly recognized tissue acidosis which seems to accompany injury. Hyperglycemia potentiates tissue acidosis and to the extent that steroids lead to hyperglycemia, they could be harmful. This has yet to be proven. While there seem to be relatively few detrimental effects of steroids, the issue still appears to evoke emotional responses, and the use of steroids should be left to the practice of the individual. Obviously, this writer is unconvinced of their utility.

The use of antacids, per NG tube, and cimetadine as prophylaxis against gastrointestinal hemorrhage has also been routine in the head injured patient. Often this use has been predicated on the presumed association of steroids and G.I. hemorrhage. It is quite obvious that gastrointestinal hemorrhage is a very frequent occurrence in those patients with severe brain injuries. However, this hemorrhage is equally frequent in those patients given steroids and those not receiving them;[1, 4] the entire issue has been reviewed by Conn and Blitzer.[3] However, gastrointestinal hemorrhage occurs extremely frequently in the severely brain injured. Much of this hemorrhage appears to be an erosive gastritis often induced by the presence of a hard nasogastric tube. While NG suction is almost always indicated in these patients, at least initially, the continued presence of a hard nasogastric tube should be minimized. If an NG tube is to be maintained in position, then it is recommended that antacids be used to titrate the pH of the stomach to 4 or above. The use of cimetadine prophylactically has been shown not to reduce the frequency of hemorrhage though there was some suggestion that the severity of hemorrhage may have been reduced, slightly, in a treated group.

The use of anticonvulsants is generally routine as prophylaxis for early seizures. The risk of seizure disorder in nonpenetrating brain injuries is generally less than 5-10% in both the long and short term. However, because the physiologic and practical consequences of an early seizure are so great, the use of prophylactic anticonvulsants is usually recommended. During an epileptic attack, the cerebral blood volume increases greatly, respiratory status is generally impaired and we have a situation where intracranial pressure may increase greatly in the face of decreased oxygen availability.

Concomitant hypertension usually maintains CPP and thus avoids most seizure related disasters. A previously unrecognized risk of seizure is hypotension, or hypotension relative to the blood pressure needed to maintain CPP, and may be induced by virtually any anticonvulsant (figure 1). Most brain injured patients can be withdrawn from anticonvulsants within the next 6-12 months.

"Standard" therapy for brain injured patients has evolved about *early* removal of a mass lesion and maintenance of an adequate blood supply to the brain.[2, 5] More recently, we have recognized that decrements in cerebral perfusion pressure may potentiate increased ICP and we have instituted protocols directed at treating the CPP.[8] Preliminary results are encouraging (figure 1).

Newer therapies directed at the accumulation of excess tissue acid, usually lactic acid, are also being evaluated at North Carolina Memorial Hospital.[9] Preliminary results are consistent with a marked reduction in the frequency of progressive, fatal intracranial hypertension. Regardless of the outcome of these clinical studies, they will only augment, not supplant, the essentials of resuscitation.

Spinal Cord Injury

Spinal cord injury has certain qualities in common with significant brain injury. Both tend to occur in the face of multiple systemic injury and are potentiated by anoxia and ischemia. Significant spinal cord injury accompanies brain injury in less than 5% of cases, but it has been standard teaching and remains so that the neurologic examination of a brain injured patient begins with a lateral cervical spine film. However, examination and resuscitation should not be delayed because of this requirement.

Spinal cord injuries can be classified according to four more or less discrete types. The first is a *transverse myelopathy* in which all modalities carried by the spinal cord are involved below the level of the lesion, i.e., posterior

column function (vibration, position, touch), motor function, and pain and temperature function are lost below the given anatomic level. The *anterior cord syndrome* is a variant of this in which spinothalamic (pain and temperature) and corticospinal (motor) function are lost in the face of preserved posterior column function. Another variation is the *Brown-Sequard Syndrome* in which only half of the spinal cord is damaged, leading to ipsilateral loss of the posterior column and corticospinal functions and contralateral loss of pain and temperature. Any or all of these can be the result of a "garden" variety cervical or thoracic fracture, and they may (usually) be partially expressed and/or coexist.

The *central cord syndrome* has a somewhat different significance. Clinically, this presents as arm weakness which is greater than concomitant weakness in the lower extremities. This seems to relate to a pathologic lesion which is characterized by ischemic necrosis in the center of the spinal cord which extends centripetally with decreasing effects toward the periphery. The arm fibers in the corticospinal tracts are located more centrally than the leg fibers (which, teleologically, gives them a shorter distance to travel to the anterior horn cells) and thus are affected first and foremost by a lesion which is centrally located. Clinically, this lesion may be associated with varying degrees of sensory loss throughout the upper and lower extremities or even painful paresthesias in both upper extremities.

It is most often due to a hyperextension injury which does *not* produce an overt fracture dislocation of the spinal cord, but whose mechanism is dependent upon hyperextension, which transiently narrows the spinal canal by buckling of the ligamentum flavum and pinching the spinal cord between this ligament and the anterior aspect of the canal. It is particularly prominent in those of the fifth and sixth decades who suffer such hyperextension injuries. A classic presentation is that of a 60-year-old alcoholic who falls, strikes his forehead, and presents with a degree of quadriparesis (arms much weaker than legs) but no overt dislocation as judged by cervical spine x-ray. Often cervical spondylosis with narrowing of the spinal canal by osteophytes is prominent. This lesion is especially important since there is no associated spinal instability and it does not require skeletal traction for fixation. It is also easily misdiagnosed as due to malingering or hysteria. A firm cervical collar such as the Philadelphia cervical collar is usually sufficient. Soft Thomas collars are not optimally effective in immobilizing the cervical spine; they represent the best that is available at the roadside, but if significant cervical injury exists, they should be replaced by traction, halo fixation or a hard collar.

If plain cervical films reveal normal alignment, then voluntary flexion-extension x-rays can be obtained. Normal films tend to reassure the examiner that a major subluxation does not exist. However, in the presence of severe pain and muscle spasm one must be aware that enough splinting can occur to reduce and temporarily maintain reduction of a cervical fracture.

Given a patient with neurologic deficit related to the spine, it is best to assume instability and splint the patient. The same tenet applies to the neurologically intact patient who complains of severe neck pain. A firm collar, sand bags, bed rest should all be utilized until a more definitive evaluation can be completed.

The key to the systemic pathophysiology occurring in the face of spinal cord injury is recognition that the parasympathetic nervous system has the majority of its outflow via the vagus nerve which exists at the skull base. The sympathetic nervous system has its entire outflow via the thoracolumbar spinal cord which courses through the cervical cord. Thus, most of the vegative signs occurring in a spinal cord injured patient relate to varying degrees of sympathetic loss with unopposed parasympathetic activity.

The first major area of concern is recognition that most of the systemic vascular resistance is a function of the sympathetic nervous system. When this is lost, the systemic vascular resistance drops to extremely low levels (figure 3). With cervical cord injuries, this loss is almost total and typical values may be 400-500 dyne-sec/cm^5 (1100 is normal). Thus, even without hemorrhage and hypovolemia, the systemic arterial pressure in a cervical cord injury patient is usually somewhat less than normal. Systolic pressures in the range of 90 (mean pressures of about 60-70) are common and reflect a massive decrease in systemic vascular resistance and generalized vasodilatation.

Because the systemic resistance decreases massively and blood pressure decreases only slightly, it is obvious that cardiac output must actually increase. Many textbooks have suggested that cardiac output is low but in fact, when this parameter is actually measured, one finds that cardiac index is increased by 50-100%. Figure 3 shows multiple cardiovascular parameters measured as part of an ongoing study of the hemodynamics of quadriplegia at North Carolina Memorial Hospital.

With the loss of sympathetic innervation to the heart and its chronotropic effects, the unopposed action of the parasympathetic nervous system (vagus nerves) leads to varying degrees of bradycardia. At times, this bradycardia is intense and may reach levels of 40 beats/min or less. This bradycardia in the face of increased cardiac index results in greatly increased stroke volume index. These effects are generally well tolerated in the young, healthy patient; however, in middle-aged and elderly patients a syndrome, which effectively mimicks congestive heart failure, can be produced. This is simply because the demands upon the myocardium are greatly in excess of its ability to perform. Any underlying cardiac disease can substantially potentiate the bradycardia due to sympathectomy and unopposed parasympathetic activity and, at times, profound bradyarrhythmias — to the point of cardiac asystole — may occur. Traditional therapy for the bradyarrhythmias has been an anticholinergic, such as atropine, 1 mg IV p.r.n. This is very effective at restoration of the cardiac rate and rhythm and also improves systemic arterial pressure as well. However, it can do nothing for systemic vascular resistance and actually may potentiate problems when systemic resistance is very low and cardiac output has already reached a maximal level.

Administration of a sympathomimetic with both alpha and beta effect (to increase systemic resistance and heart rate simultaneously) appears logical and is, indeed, effective. Dopamine, often at lower than expected doses, tends to be very effective at improving systemic resistance, sys-

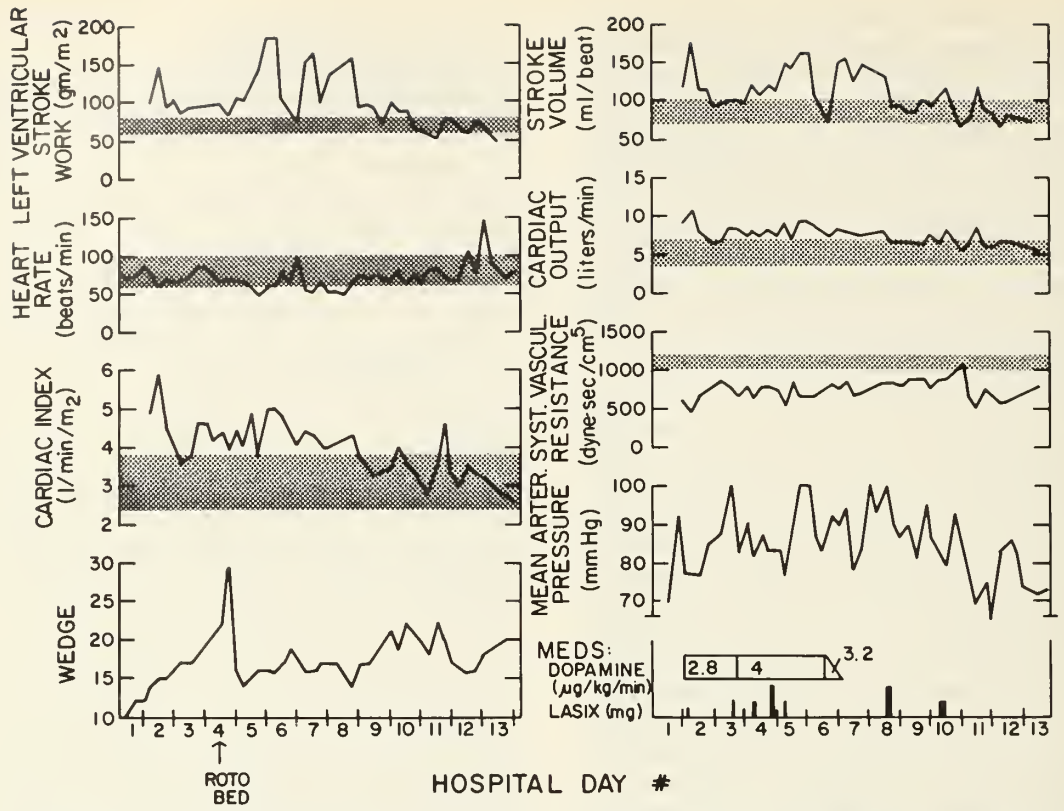


Figure 3. *This is a complex plot of the hemodynamic consequences of high quadriplegia. The important points are that systemic vascular resistance was extremely low in this patient and cardiac index was nearly twice normal. These changes gradually reversed with time but may have profound effects before they begin to resolve. This patient required the use of low dose dopamine to help stabilize his cardiovascular responses and actually showed a decrease in cardiac index with institution of a small amount of dopamine which helped increase his systemic vascular resistance. Because of rising pulmonary artery wedge pressures and hypoxemia and the development of a respiratory distress syndrome on day 4, diuretics were instituted and he was placed on an oscillating bed.*

temic pressure, and heart rate (figure 3). A pure alpha agonist does have some role when the heart rate is acceptable (especially likely in mid-thoracic spinal cord injuries. Here the primary problem is loss of peripheral vascular tone and low doses of phenylephrine, or a similar alpha agonist, are effective.)

Of equal importance is the respiratory system. All cervical spinal cord injuries of significant degree are associated with paralysis of the intercostal musculature. The intercostal musculature splints the chest such that the diaphragm can effectively expand the lung and provides respiratory excursion when more than the diaphragmatic motion is required. Loss of the intercostal function results in a tremendous decrease in both tidal volume and negative inspiratory force. Typical parameters for a mid to low cervical quadriplegic are negative inspiratory force of less than 25 cm H_2O and tidal volumes of 300 to 350 cc. Respiratory rate is unaffected and will often be higher than normal. Effective coughing and mobilization of secretions is extraordinarily difficult but is usually not an issue in the emergency room situation. However, within 24 hours it shall become one.

On admission, the pulmonary shunt fraction is usually 15-25%, which is in the range of severe impairment. Within 24-48 hours, this quotient will generally increase to 30-50%. This implies that the rapid development of hypoxemia will occur within the first day or two after a significant cervical spinal cord injury. Two courses of action are thus permitted. The first is prophylactic intubation and mechanical ventilatory support to maintain expansion of the alveoli and prevent successive and progressive alveolar collapse and atelectasis. The second is massive and aggressive pulmonary toilet instituted from the time of admission with concomitant and frequent (q4-q8h) bedside measurements of the vital capacity, tidal volume, and negative inspiratory force. A relatively new aspect of pulmonary toilet is the use of the oscillating bed (Kinetic Therapy Table or Roto Rest Bed). The rocking motion of the bed favorably affects ventilation-perfusion abnormalities and can markedly improve pulmonary shunt fraction (Qs/Qt) (figure 4). The improvement in Qs/Qt may be sufficient to avoid intubation in otherwise marginally compensated patients.

Intubation should be electively instituted (preferentially nasotracheal) given progressive deterioration in these values and/or the development of hypoxemia. It is preferable to institute intubation when these parameters are clearly worsening rather than wait for the development of a full-blown respiratory arrest, pneumonia, and/or diffuse atelectasis. Once established, these processes are very dif-

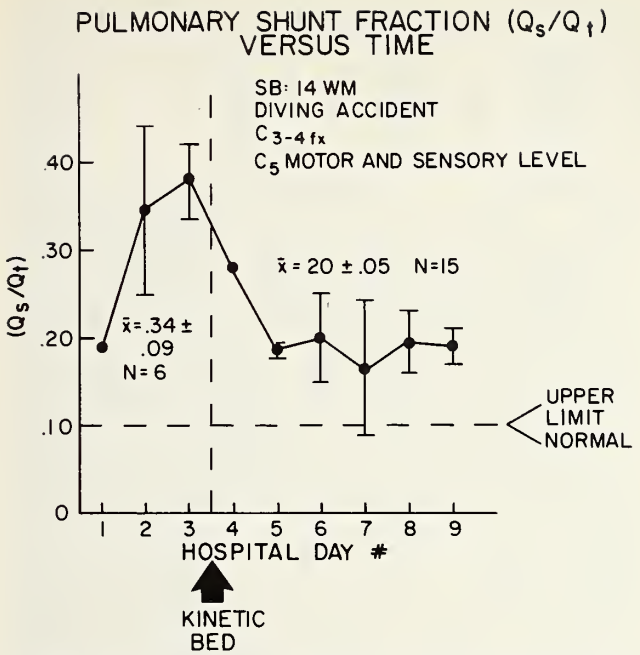


Figure 4. *This is the same patient as shown in figure 3. On admission, his pulmonary shunt fraction was somewhat less than 20%. This rapidly increased over the next 36 hours to nearly 40% with some values reaching 50%. He was placed on an oscillating bed and independent of any other therapeutic measures, his shunt fraction gradually and rapidly declined to the region of 20% and below. He remained stable at these lower levels thereafter.*

ficult to manage in the quadriplegic compared to the relative ease with which they are prevented. Because of the incipient pulmonary difficulties with high spinal cord injury, atropine, with its drying effect upon pulmonary secretions, is not recommended; while atropine may be lifesaving in the acute bradyarrhythmia, a sympathomimetic for such cardiac problems is doubly preferential.

Another major area affected by the autonomic nervous system in acute spinal cord injury is the gastrointestinal system. Loss of sympathetic tone and profound unopposed vagal activity results in noncoordinated activity of the gastrointestinal tract and the development of ileus. Since this is associated with continued activity of the gastrointestinal system (though uncoordinated), near normal bowel sounds are usually present but are misleading in the capacity of the bowel to accept enteral feeding. It may be 24-72 hours before bowel sounds disappear in the acute cervical spinal cord injury. However, if early feeding is undertaken, the ultimate development of ileus does not seem to be mitigated, but is worsened. In high cervical cord injury, a profound ileus with gastric and abdominal distention, which further increases upward pressure upon the diaphragm and decreases pulmonary reserve and function, is the rule rather than the exception. This author recommends withholding enteral feedings for 5-7 days. In lower cervical cord and thoracic injuries this period may be shortened, and in very low thoracic or lumbar lesions without significant intercostal paralysis ileus is much less of a problem and the consequences of its development, in terms of the pulmonary status, are much less severe.

Along with other pyramidal functions, the bladder and sphincters are often paralyzed. There are two primary approaches to acute bladder care. One is intermittent catheterization of the bladder on a q2-q4 hourly basis. This avoids semipermanent or permanent instrumentation of the bladder and helps reduce the risk of infection, but is predicated upon the availability of personnel with training to perform this procedure with the frequency required. Many paraplegics and quadriplegics will ultimately develop a spastic bladder which becomes automatic and empties reasonably well. However, if the urine volumes removed by intermittent catheterization are very large, as they may be if catheterization is not frequent enough, then a stretch injury to the bladder (which may be permanent) can result. If volumes removed by catheterization begin to exceed 350-400 cc, then the catheterization schedule must be adjusted. Again, this requires a mildly sophisticated and adequately staffed nursing group. The other less desirable but often more practical alternative is continuous catheterization. This may be medically indicated if problems with urinary output, congestive failure, sepsis, or the other problems associated with acute spinal cord injury or multiple trauma co-exist and make hourly urinary output desirable. This author recommends continuous Foley catheter from admission for at least 48-72 hours.

With significant spinal cord injury comes cutaneous anesthesia combined with paralysis. The central issue here is the potential development of decubitus ulcers, which significantly prolong hospitalization for these individuals. Frequent turning of the patient q1/2-q1 hour is mandatory. This improves the pulmonary shunt fraction because it helps improve ventilation-perfusion inequality in the lung which is the basis of this dysfunction. As noted, the introduction of oscillating beds, which continuously rotate the patient through a high degree of arc, has offered some assistance to nursing personnel. Skin care is improved and made easier, and at the same time the pulmonary status of the patient is significantly improved.

The use of skeletal traction, halo fixation, and early vs. late surgery for cervical fusion and/or mobilization remain rather controversial and are often dictated by regionally available neurosurgical and orthopaedic personnel. Most unstable cervical fractures, however, are treated with some degree of rigid immobilization while cervical spinal cord injuries characterized by bony stability (such as that which is typical of central cord syndrome) may often be treated with a firm cervical collar, such as the Philadelphia collar.

Specific Guidelines

It is worthwhile to remember a few basic principles, particularly when one is encountering a major brain or spinal cord injury in the middle of the night. One-half of the patients presenting with severe head injuries have significant alcohol levels in their blood. The presence of alcohol does not rule out a brain injury. It should not be used to explain a depressed or abnormal neurologic status nor the inability to follow commands for this will rarely be the case. Rather, the assumption should be that mechanical brain injury and/or mass lesion exist until proven otherwise. Most "drunks" can follow commands.

Begin the exam of a comatose patient with a lateral cervical spine x-ray. Do not delay the exam. It is not

necessary to move the neck to ask a patient to wiggle his toes or squeeze the physician's fingers. In particular, do not delay fluid resuscitation and adequate ventilation of the patient for fear of a cervical spine injury.

As a mass lesion develops in a reasonably awake patient, agitation and combativeness often precede depression in the level of consciousness. This agitation and combativeness must not be confused with or explained away as intoxication; it will usually precede the development of a dilated pupil. By the time pupillary dilatation has occurred, the development of a mass lesion and intracranial decompensation has usually progressed quite far. The best time to salvage these individuals is before this progression occurs.

Given a patient who is demonstrating abnormal extension or abnormal flexion (decerebration or decortication) but who has intact pupillary and oculocephalic reflexes, this disturbance in consciousness is usually metabolic in origin. Profound hyperglycemia or hyopoglycemia, anoxic injury, and toxins will often be shown to be the basis for this condition.

Lastly, resuscitation of the brain injured patient requires precisely the same techniques as the abdominal or chest injury. The major difference is time. The brain is less tolerant, more demanding and less forgiving than most other organ systems. However, the rewards of dealing with these issues well are great.

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SCIENTIFIC ARTICLE

North Carolina Statewide Trauma Center Outreach Program

Joseph A. Moylan, M.D. and Joyce C. Pressley, M.P.H.

• *A description of a program to familiarize community hospitals with the state's Level I trauma centers.*

THE emphasis on emergency medical services in the past decade has resulted in significant improvements in medical care for the severely injured patient. Initial efforts focused on prehospital care and were successful in achieving higher standards for education and certification of personnel and for improvements in equipment and transportation. This was accomplished over a decade and a half largely through the efforts of the North Carolina Office of Emergency Medical Services. In more recent years, attention has focused on hospital care, particularly on the development of a trauma system to assure care appropriate to the level of injury regardless of geographic location of the patient. These efforts led to the development and designation of specialized care centers for the treatment of critically ill and injured patients. In 1982, three institutions were designated as Level I or Statewide Trauma Centers: Duke University Medical Center, North Carolina Memorial Hospital and North Carolina Baptist Hospital.

Due to the close geographic proximity of their respective trauma centers and the resulting overlapping patient catchment areas, Dr. Herbert Proctor of North Carolina Memorial Hospital and Dr. Joseph Moylan of Duke Medical Center jointly developed a program to familiarize medical communities with the concept and capabilities of Statewide Trauma Centers and to improve the day-to-day relationships of the trauma centers and the community hospital. The first step of this joint effort, now known as the Trauma Center Outreach Program, was to develop a better understanding of the problems faced by the thirty-one community hospitals located in the 27 county area comprising the base referral area for the two medical centers. The program currently being pilot tested in this 27 county area was designed to assist referring institutions in making rapid assessments and in transferring the small percentage of patients needing resources unavailable at a community hospital. An education program utilizing audiovisual aids and brochures was developed to present to emergency department personnel in the outlying hospitals explaining the function of a Level I Trauma Center, what specific services and resources a statewide trauma center offers, how to efficiently and rapidly contact appropriate personnel within the center to expedite referral and how to select and prepare patients for a safe transfer.

The circumstances relating to the patient transfer and the problems faced by the referring community hospitals were assessed using a questionnaire which was completed by community hospital emergency department personnel. This questionnaire also served to identify staff interest and the perceived need of a trauma education program. Specific questions were included to determine the criteria utilized by the community hospital in transferring patients and patient types always or nearly always transferred. Most importantly, results of the questionnaire would provide information on what the Statewide Trauma Center could do to facilitate the patient transfer and what information the referring hospital would like returned following the transfer. Questionnaires completed by these hospitals indicated that the majority of these institutions always or nearly always transferred serious trauma patients to one of the Statewide Trauma Centers. They indicated a need for additional trauma education, as less than twenty percent of the facilities reported inhouse educational programs on trauma care. Many referring hospitals requested an educational program on preparation of the patient prior to transfer and specific information on what laboratory data or other tests should be done before transfer. All institutions indicated a need for a contact within the trauma center for efficient and rapid patient acceptance and follow-up information.

A grant from the Office of Emergency Medical Services provided the financial impetus to undertake and develop this project. The two hospitals developed an educational packet for state application including a slide presentation on Statewide Trauma Centers, handouts and presentations on the utilization of standardized triage and transfer protocol and a follow-up program. The program identified guidelines directed at early identification of trauma patients requiring transfer to a Statewide Trauma Center, protocols for the treatment of trauma patients prior to and during transfer, organized procedures for facilitating transfer to a Statewide Trauma Center and a timely follow-up system for providing feedback to the referring facility concerning the patient's progress.

Identification of Patients for Transfer

The decision to transfer a trauma patient to a Statewide

From the Department of Surgery, Duke University Medical Center, Durham 27710.

Trauma Center is based on two triage protocols or the diagnosis of injuries requiring special resources. The Trauma Score, developed by Dr. Harold Champion and associates,[1] provides a simple instrument to quickly assess the severity of injury and predict mortality. This system has been widely implemented and found to correlate well with severity of injury and the need for specialized care (figure 1). The Trauma Score is a numerical grading system for estimating the severity of trauma. The score is composed of the measurements of cardiopulmonary function as well as a modified Glasgow Coma Scale. It has been shown that mortality rates increase significantly with progressively lower scores (figure 2). This index allows rapid identification of high risk patients without the need for specific diagnosis.

Another approach to triage is the Anatomical Diagnosis Categories developed by the American College of Surgeons Committee on Trauma. Utilizing this system, patients can be identified as being appropriately cared for at a community hospital (category II or III injury) and those patients with a category I injury who should be transferred to a Statewide Trauma Center (table 1). Modifications in these categories include age (either very young or very old) or preexistent medical conditions; these subclasses of patients may benefit from care at the Statewide Trauma Center.

There are certain injuries that may not be life threatening, but which require the special resources available at a Statewide Trauma Center. These include significant eye

Trauma Score

The Trauma Score is a numerical grading system for estimating the severity of injury. The score is composed of the Glasgow Coma Scale (reduced to approximately one third total value) and measurements of cardiopulmonary function. Each parameter is given a number (high for normal and low for impaired function). Severity of injury is estimated by summing the numbers. The lowest score is 1 and the highest score is 16.

Respiratory Rate	10-24/min	4	
	24-35/min	3	
	36/min or greater	2	
	1-9/min	1	
	None	0	A =
Respiratory Expansion	Normal	1	
	Retractive	0	B =
Systolic Blood Pressure	90 mm Hg or greater	4	
	70-89 mm Hg	3	
	50-69 mm Hg	2	
	0-49 mm Hg	1	
	No Pulse	0	C =
Capillary Refill	Normal	2	
	Delayed	1	
	None	0	D =

Glasgow Coma Scale

Eye Opening	Spontaneous	4	**Total Glasgow Coma Scale Points**
	To Voice	3	
	To Pain	2	14-15 = 5
	None	1	11-13 = 4
Verbal Response	Oriented	5	8-10 = 3
	Confused	4	5- 7 = 2
	Inappropriate Words	3	3- 4 = 1
	Incomprehensible Words	2	
	None	1	E =
Motor Response	Obeys Command	6	
	Localizes Pain	5	
	Withdraw (pain)	4	
	Flexion (pain)	3	
	Extension (pain)	2	
	None	1	
Total Trauma Score		(A+B+C+D+E) =	

Figure 1.

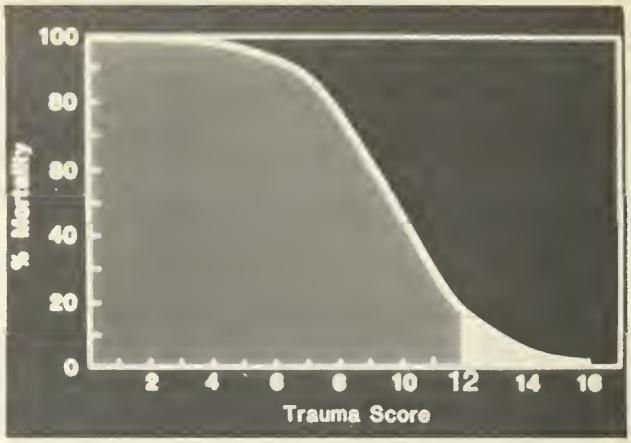


Figure 2.

injury, soft tissue damage requiring plastic surgery, partial or complete amputation with the need for microsurgical repair or reimplantation, and critical burns. Utilizing the American Burn Association's criteria for disposition of burn patients' critical burns, i.e., those with second degree burns over greater than 25 percent of the total body surface, third degree burns of the face, hands or feet and complications of burns especially respiratory tract injury, should be treated at a special facility.

Treatment Protocols

Once the decision is made to transfer a patient, treatment protocols have been developed to insure proper stabilization and safe transfer. Important aspects of these treatment protocols include airway stabilization and maintenance through the use of endotracheal or cricothyroidotomies with oxygen therapy, the use of adequate fluid prior to and during transport to maintain blood pressure of at least 90 mm Hg, and the use of MAST trousers to augment fluid resuscitation (figure 3).

Specific injuries require additional therapeutic maneu-

Table 1
Anatomical Diagnosis Categories

CATEGORY I PATIENTS

- combined system injury
- open fracture
- uncontrolled hemorrhage
- blunt abdominal trauma with hypotension
- neurological injuries
  - unconsciousness
  - posturing
  - paralysis
- severe maxillofacial injuries
- unstable chest injuries
- pelvic fractures
- penetrating abdominal wounds
- severe head, neck and upper respiratory tract injuries

CATEGORY II PATIENTS

- open or closed fractures
- soft tissue injuries with stabilized bleeding
- multiple rib fractures
- blunt abdominal trauma without hypotension
- transient loss of consciousness

CATEGORY III PATIENTS

- uncomplicated fractures
- no hypovolemia or hypotension
- no neurological injuries
- chest injuries without respiratory distress

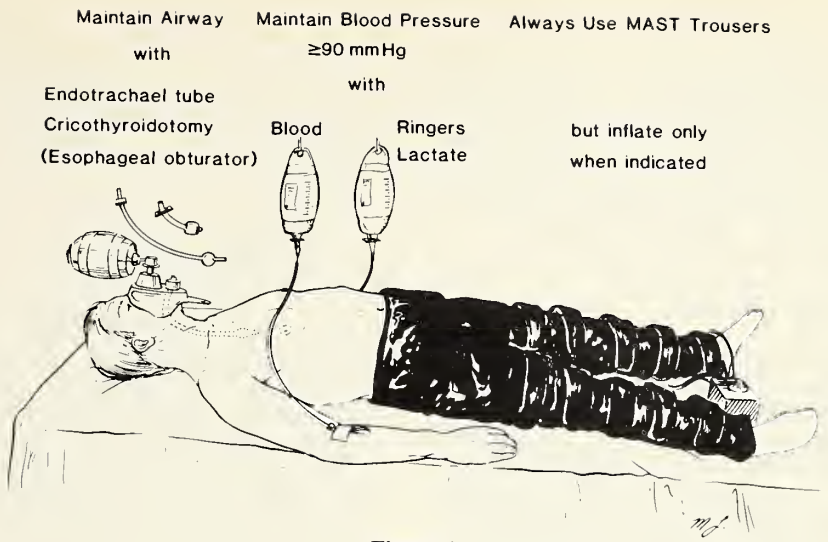


Figure 3.

Transfer Flow Chart

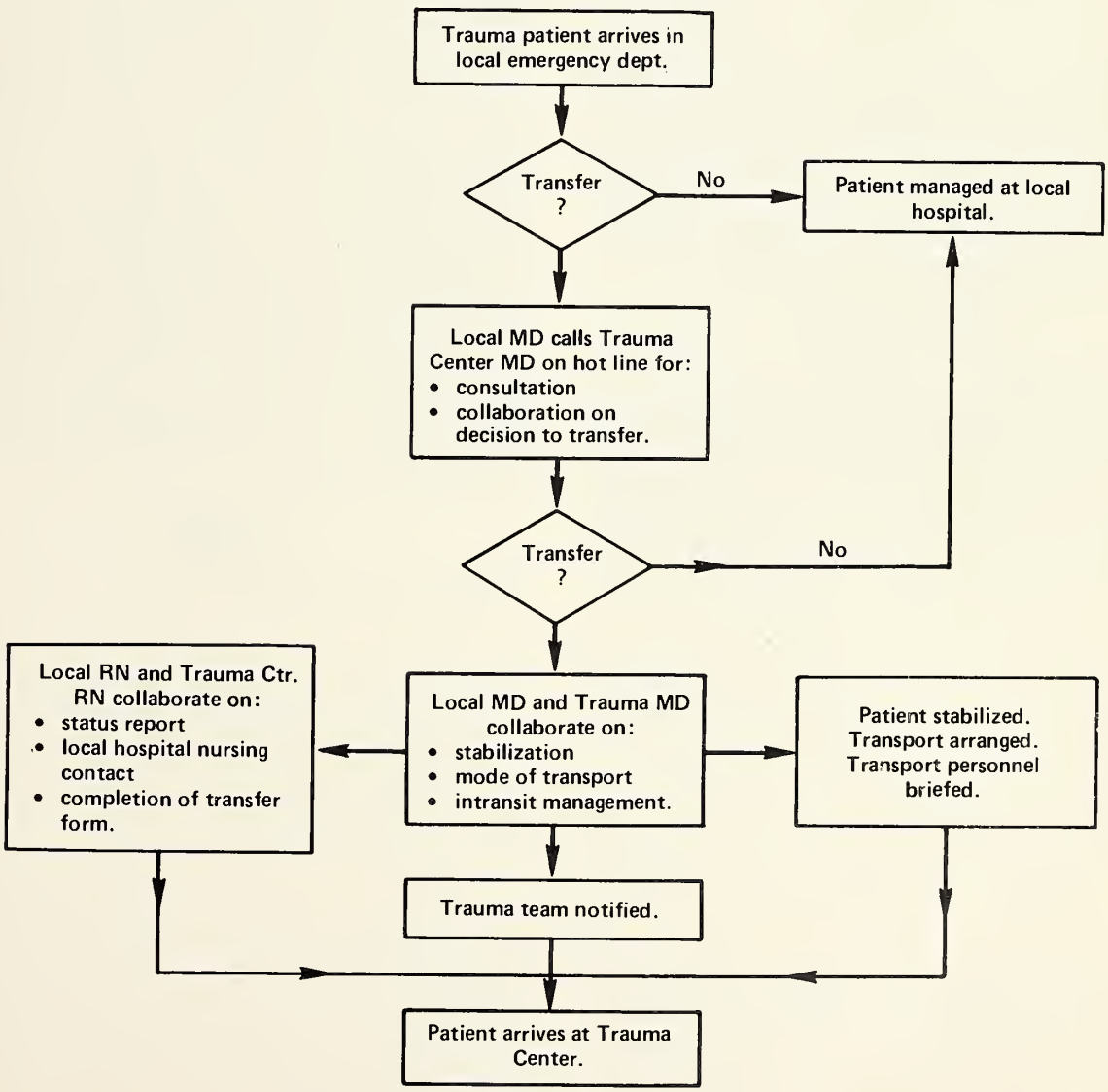


Figure 4.

vers prior to transport. Neurologic injuries should receive ventilatory support, stabilization with a cervical collar, back immobilization and nasogastric decompression. Chest injuries with specific complications such as hemopneumothorax may require chest tube placement. Flail chest requires ventilatory support and cardiac tamponade requires pericardiocentesis. These treatment protocols also contain information on stabilization of abdominal, soft tissue and burn injuries.

Transfer Procedure

Transport should be arranged once initial stabilization is begun. During the transport phase, continued care should be provided. In order to facilitate and provide consultation for the initial stabilization and transfer, special telephone lines have been installed in the emergency departments of both Duke University Medical Center and North Carolina Memorial Hospital to handle communication pertaining to trauma patients requiring transport to these centers. These telephones (DUMC 1-800-672-2538 and NCMH 1-919-966-3333) are manned 24 hours a day by a physician with trauma care skills. This allows direct physician-to-physician contact early in the trauma patient's treatment course.

As the transfer is evolving, the goal should be continued support of the respiratory and circulatory systems during transport. Adequate volume replacement during the transfer, continued monitoring of vital signs and use of appropriate drugs are emphasized. Additional communication with the Statewide Trauma Center by phone allows periodic updates on the estimated time of arrival and any significant changes in the stability of the patient (figure 4).

Follow-Up System

One of the important outcomes of the Trauma Center Outreach Program was the development of a system to provide feedback to the referring physician concerning the patient's progress. Previously, patient information including discharge summary was often sent to the patient's primary physician. Under the new follow-up system (figure 5), information will be provided both to the patient's primary physician as well as the emergency department physician who referred the patient. This allows communication between the referring emergency department and the Statewide Trauma Center, thus reinforcing the effectiveness of the triage and treatment protocol.

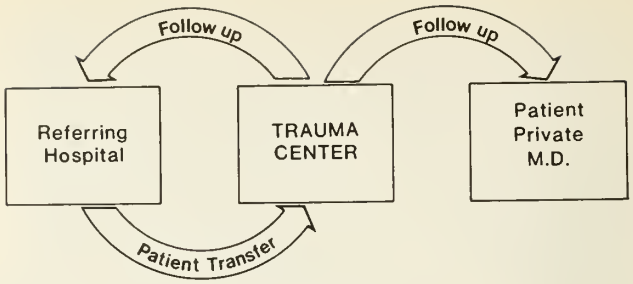


Figure 5.

Future of the Trauma Center Outreach Program

At the present time, programs have been presented to approximately two-thirds of the community hospitals in the North Carolina Memorial Hospital and Duke University Medical Center referral catchment area. An extensive evaluation process of the demonstration program has included evaluations of the educational presentations for their organization, content and effectiveness; the ability of the program to increase the number of critically ill and injured patients who are appropriately stabilized and managed; the overall effectiveness of feedback provided to the referring hospitals; and the success of increasing the confidence with which trauma patients are transferred.

Based on this evaluation, alterations are being made to improve the program and eventually disseminate it for use by other trauma centers within both North Carolina and other states. The ultimate goal of this program is to provide the nurse and physician in the emergency department with the information they will need in order to readily identify those individuals who can best be cared for in a Statewide Trauma Center as well as increasing the accuracy and confidence with which the emergency department personnel make this judgment.

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SCIENTIFIC ARTICLE

Trauma Care Delivery in Eastern North Carolina

Larry S. Lewis, M.D.

• *A presentation of the options for improving care of trauma victims in the rural parts of Eastern North Carolina.*

IN recent years, trauma has become recognized as a major national health problem and economic burden. What has not been adequately emphasized or appreciated is the component of this problem contributed by rural areas. Although 70 percent of the nation's population now lives in urban areas, up to 70 percent of our trauma fatalities still occur in rural areas.[1] The fatality rate for rural motor vehicle accidents remains four to six times that of comparable urban injuries.[2-4]

Eastern North Carolina, a primarily rural 29 county area with a population of 1.5 million, certainly shares many common problems with other rural sectors of the United States: 1) long distances from regional trauma facilities; 2) access to emergency transport capabilities; and 3) preparedness of local physicians in early care of the injured patient.

The Pitt County Memorial Hospital and the East Carolina University School of Medicine and their staffs have recently assumed the responsibilities of the Level II Trauma Facility for this underserved region. The responsibilities of this require that we address the above concerns.

The geography of eastern North Carolina does little to aid in the rapid and efficient delivery of emergency trauma care. Large distances are frequently involved from the site of injury to the place of initial care. Injuries frequently occur in isolated settings where both communication and transportation are impeded. The routes of travel are far from the super highways of the urban setting. This all serves to delay the early care of the injured patient and certainly interferes with rapid ground transportation to higher level trauma facilities.

Two possible solutions to this problem immediately come to mind: 1) air evacuation; 2) improved ground transportation.

The first of these, air evacuation, has some positive and negative aspects. On the positive side, many studies have been reported in the literature attesting to improved survival statistics for the air evacuated patient but these are frequently difficult statistics to evaluate in terms of comparable patients handled by ground transportation. In addition air transportation may serve as an important patient referral source, a clear positive in this era of competition for a decreasing patient census.

On the negative side, high start-up and operating costs are the major deterrents to initiation of this service. The first step that any hospital should take before establishing an emergency helicopter service is to conduct a thorough feasibility study. This study should include an analysis of projected utilization, a review of clinical resources and an evaluation of costs.

Approximately 70 percent of the cost of operating a helicopter service is fixed, so it is essential for the hospital to maintain a minimum number of flights. Each hospital must carefully survey its own situation prior to instituting a helicopter service.

The second drawback, ground transportation, also involves large capital outlays, but no single source is required to bear the burden so these costs are more easily distributed. In addition it can expand in small increments once the basic framework is already in existence. The main disadvantages of ground transportation are access to the injured and time of transportation.

Although there may be some disagreement regarding the best form of transportation there is little question regarding the most important ingredient for future expansion and growth of eastern North Carolina's regional trauma care: the wider and mandatory certification in Advanced Trauma Life Support, as outlined by the American College of Surgeons. Currently there remain deficiencies in the early care and treatment of the injured whether one works in the large or small hospital. We can all improve our performance through proper application of the techniques outlined in the ATLS course. Making this a requirement for all physicians working in emergency departments would not only enhance care of the critically injured but would also improve care of the less severely injured and perhaps lessen the overall morbidity of trauma and deliver a more stable and potentially salvageable patient to regional care facilities.

Our main emphasis is placed on physician education. Neither air nor ground evacuation is as rapid and smooth as portrayed, and both require sophisticated support. Both are only as good as the initial triage and treatment allow. All injured patients would benefit from a better trained, more sophisticated physician population. Lastly, better injury care is still only as good as the human component.

We should not be caught up in the glamour of high speed transport and fancy equipment and lose sight of the multitude of lesser injuries that exact a large cost to our state, in both monies and suffering, but instead should build a sophisticated regional trauma system based on good initial care and an expedient long distance transport.

From East Carolina University School of Medicine, Greenville 27834.

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SCIENTIFIC ARTICLE

The Interagency Incident Management System: An Important Element in Successful Prehospital Emergency Medical Care

Herbert Garrison and Thomas Griggs, M.D.

• *This paper describes a simple interagency incident management system that provides for the safety of emergency personnel as well as for planning and coordination of resources at emergency scenes. Control and coordination provided in this manner can mean the difference between life and death to both patients and rescuers.*

THE prehospital care of trauma patients in North Carolina has improved greatly in the past ten years. In many localities, emergency medical technicians are capable of performing sophisticated medical procedures including volume resuscitation and advanced cardiac life support. The training of these technicians has been predominantly technical and has been provided in large measure by medical professionals. Many, if not most, of these trainers have had little or no experience in providing prehospital care. Those who have functioned to some degree in the field have been impressed with the difficulty of controlling the emergency scene so that patient care can proceed as it is expected to in a hospital setting.[1] The need to gain and maintain control of the emergency scene is, therefore, becoming recognized. Unfortunately, the mechanisms by which such control can be achieved are not widely known nor practiced. This paper will illustrate efforts in Orange County, North Carolina to develop and use a simple incident management scheme. It is designed to be used by all of the emergency agencies in the county to provide the control and management in the field that is recognized to be the crucial first step in determining the eventual outcome of patients involved in emergencies.

Case Illustrations

The need for management at the scenes of emergencies can be illustrated to some degree by the following case reports.

The most critical goal of a scene management system is to provide safety for the emergency medical and other emergency personnel working with the emergency. Many examples can be given to describe tragic accidents occurring to emergency personnel as a result of their unknowing entry into hazardous environments.

Case 1: An ambulance was summoned to the basement of the Pharmacy School on the campus of the University of North Carolina at Chapel Hill. The caller reported that she thought a victim had suffered a heart attack and was unconscious. Upon arriving at the scene, the two paramedics entered the basement of the building as directed by bystanders and found a male patient on whom two occupants of the building were performing cardiopulmonary resuscitation. Immediately upon the arrival of the ambulance team, the citizen rescuers stepped back, reported that they were ill, and staggered from the building. The paramedics began immediately to assess the patient and to continue cardiopulmonary resuscitation. They noticed a strange odor in the room, and they quickly developed headaches and nausea. Within a few minutes, a safety officer from the University entered the building wearing self-contained breathing apparatus. The patient was successfully resuscitated from ventricular fibrillation and transported to the hospital. The paramedics were ill for a short period but recovered without treatment.

Review of the incident indicated that the patient had been the victim of a large chloroform spill that had occurred in a room only several feet from where the paramedics assumed his care. The fact of the spill had not been reported to the person who in turn called the 911 emergency operators.

Failure to assign responsibility for safety at the scene to one paramedic could have, in this case, cost both of them their lives. Under the Orange County incident management scheme, the first arriving emergency unit at an incident assumes "command." The first task of command, in turn, is to view the scene and to make other observations and determinations as necessary to insure the safety of all of the emergency personnel on the scene or reporting to the scene. Subsequently arriving units allow this assessment to be made by assuming a "staged" position several hundred feet from the scene until assigned to duties at the scene by the command person. Assumption of command by standard procedure, assigning security functions to command as a high priority responsibility, and supporting the safety and security priority by the use of staging for subsequently arriving personnel allows control at a scene to be established as an initial event.

From the Division of Cardiology, University of North Carolina School of Medicine, Chapel Hill 27514.

Case 2: The second major goal of an incident management program is to coordinate activities so that people and other resources are used as efficiently as possible. This requires the development of a plan or strategy, and the deployment of people and equipment according to that plan. The following case represents an example of the need for such a plan.

A small, single engine aircraft with four passengers and a load of fuel and luggage attempted to depart from the Horace Williams airport in Chapel Hill. The plane developed insufficient power to clear the runway, banked to the left, and crashed nose down into a field. The crash was witnessed, and rescue, fire and police agencies were dispatched. The crash caused major injuries to all four occupants of the plane. The injuries involved head trauma as well as major chest, abdominal and extremity injuries. Several paramedics, additional emergency medical technicians, police personnel trained and certified as emergency medical technicians, and two physicians were at the scene within several minutes. Extrication progressed rapidly. The patients were then placed in an area where they were separated by the airplane debris and by distances of up to 50 feet. Medical equipment was scattered throughout the scene. Devices such as blood pressure cuffs were moved from one patient to the next. The two physicians made rapid evaluations on two of the patients but knew nothing of the conditions of the other two. The patients were treated by the EMTs and paramedics who first encountered them. No effort was made to establish by priority the order of transport of the patients, and the physicians at the scene were used ineffectively. Finally, considerable problems occurred with transport because police officers were unable to assume that they had permission to ride with patients in the ambulances.

This case illustrates a common event in emergency medicine. A major accident occurred and caused a number of serious injuries to a relatively small number of patients. Sufficient manpower and equipment were at the scene within minutes, yet they were used less effectively than appropriate.

Many authors have written of the need for a special strategy for managing major incidents such as this.[2, 3] That strategy involves four main elements: 1) "triage" to identify salvageable patients with need of immediate care, 2) "extrication" from the immediate incident scene to a treatment area in a centralized place, 3) "treatment" in the field treatment center, and then 4) "transportation" of the patients according to a priority based upon the extent and survivability of their injuries. Unfortunately, such a strategy requires judgments based upon good management procedures. In many communities, as in ours at the time of this incident, the knowledge of such a strategy fails to bring about the implementation of the strategy. This is because no system is in place to provide for a person who 1) will make the decision that that strategy will be followed, and 2) will gain control of incoming resources so that they can be deployed according to that strategy. In the system now in place in Orange County, the command officer's function is to establish a simple "strategy" or plan and then to support the plan by placing people into manageable teams and assigning them definable tasks. To establish a strategy, the command person is expected to consult with as many people as necessary. In fact, in the situation described above, the command officer would probably have been a fire officer who would have appointed a medical officer to establish medical strategy and set it into operation. The teams, in turn, would have been formed in a staging area and then deployed in "sectors," probably named "extrication," "treatment," and "transportation."

The Incident Management System

The incident command or management system adopted in Orange County is patterned after that used by the National Interagency Incident Management System.[4, 5] The Orange County incident management system is based upon a set of standard operating procedures used by essentially all of the emergency agencies in the county. The standard procedures outline the following basic components of the system:

1) At every incident where more than one agency responds, the first arriving unit is responsible for establishing command. Command, obviously, may then be transferred up a chain of command as appropriate. However, the designation of command implies that throughout the emergency, the functions of management will be focused on one individual.

2) The system further provides that the function of this management program is to provide for what we call "the five S's" — 1) security, 2) staging, 3) strategy, 4) sectors, and 5) support. The case illustrations describe the characteristics of the first four of these functions. The provision of support in the management system involves supply, communications, public relations, and other elements that may be needed as resources to manage an emergency incident smoothly and efficiently.

The establishment of the system in Orange County has evolved over several years after initial stimulation by discussions of incidents such as those described above. These discussions involved not only emergency personnel but community management and political leaders as well. The medical community and specifically the Disaster Committee of the North Carolina Memorial Hospital were deeply involved in the planning and practicing that led to the establishment of the system. The program now is coordinated by the county's Emergency Services Director. This person chairs a committee referred to as the "Command Team." This team comprises the chief and assistant chiefs of every emergency agency in the county, the elected officials, the county and town managers, and the emergency department and security chiefs from the hospital. The team meets as a whole at least every two months. The team includes, as well, several subcommittees, which meet more frequently. The meetings involve critiques of incidents, training in command functions, and planning. The command team also coordinates at least four major disaster drills each year and sponsors command and mass casualty management programs that are presented as training units to the individual agencies on a regular basis.

The incident management program has affected all aspects of prehospital emergency care in Orange County. Its major effect has been to bring about better cooperation

and coordination between the agencies. A single case illustration makes this point.

Case 3: A college student and her boyfriend were arguing violently in a local apartment house. The girl's brother came to check on her and in an ensuing argument was shot in the abdomen. The assailant fled to a nearby apartment. The dispatch center dispatched police and rescue units. The first public safety officer on the scene reported that he had a victim and a witness who had seen the assailant in the area with the gun. He established command and advised the rescue unit to stage one block away. By way of radio, he then deployed a team of officers to secure the apartment where the victim was reported to be. Those officers, having been assigned by command, then reported the apartment secured, asked that the rescue unit be sent forward, and remained with the rescue unit while paramedics assessed and treated the patient. A second team of officers was assigned to pursue and arrest the assailant. This was accomplished within several minutes. Further responding officers were asked to secure the streets in the area and to deal with the neighbors who by this time were beginning to assemble. Command was transferred within a few minutes to the police patrol supervisor who secured the crime scene as the victim was removed and called for investigators and photographers.

This case illustrates the functions of security, staging, strategy, sectors, and support. It also demonstrates the important coordination and cooperation aspect that an interagency incident management system can provide.

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North Carolina Medical Journal

Features for Patients November 1984

SEAT BELTS PAY OFF

B. J. Campbell, William Hunter, and Marianne Gemming

Did yau knaw that a seat belt can save yaur life? Did yau knaw that wearing belts can win yau prizes?

A research praject applying behaviar theary was canducted in Chapel Hill and Carrbara ta increase the use af vehicle safety belts. The Highway Safety Research Center at UNC was funded ta determine whether a widely advertised seat belt campaign cambined with varius incentives would result in greater seat belt usage.

Seat belts are the single most cast effective way ta reduce matar vehicle deaths, the leading cause af death far all persans under 34 years af age.[1] Narth Caralina crash data shaw that death amang frant seat passenger car occupants is reduced by 60-65% amang belted campared with unbelted accupants cantralling far severity af the crash. Likewise, seriaus injuries are reduced by abaut half when accupants are praperly restrained.[2]

Yet belt use has never been very high in the U. S. Natianally, belt use is naw estimated at 13%.[3] In Narth Caralina, use amang crash victims is abaut 5%.

Ta date, efforts ta increase use thraugh publicity campaigns have nat shown much success although, ta be fair, nat a great deal af resources have been devated ta this in the past.[3] In cantrast, nearly 30 other cauntries and states have traffic laws requiring belt use,[4] much like recently enacted child restraint laws naw in farce in 46 U. S. states.[5] In mast fareign cauntries with belt-use laws, belt use is quite high. In Australia, belt use in Melbaurne is aver 90% in the daytime urban setting, and is never much lawer than 60%.[6]



A contest logo and slogan were used throughout the campaign. The message was "Seat Belts Pay Off" in lives saved, in injuries reduced and, during the campaign, in contest prizes.

Graving aut af the wark af B. F. Skinner, the idea af using rewards to strengthen behaviar has by naw had cauntless applicatians. The idea af randamly rewarding belt wearers has been tried in several clased settings like high schaals ar factaries. Indeed, in 1982 a praject at the Chapel Hill High Schaal achieved a maximum 70% wearing rate based on the randam allacatian af 300 five-dallar prizes.[7] Even at the end af the schaal year belt wearing rates held at 45% (up fram a baseline of 19%). Rates have held far this schaal year at 45-50% by the ance-a-week allacatian af rewards danated by parents and the PTA. A 52% shaulder belt wearing rate was seen the final week af schaal. Based an previous data, we estimate that added lap belt use brings the tatal restrained ta 60% ar

Fram the Highway Safety Research Center, University af Narth Carolina Statewide Trauma Center, Chapel Hill 27514.

greater. Similor results have been demonstroted in 10 or sa ather work place settings.

The idea of the current project wos to leorn whether the same techniques will work in the much larger setting of o whole community, where it is more difficult ta moke people oware of the compoign ond therefore more difficult to reinforce the benefit to belt wearing. In a setting like o school or foctary essentially everyone knows obout the effort, ond olso neorly everyone will repeatedly see the incentive-giving teom ot work neor the factory or school gotes. In the community at large, both of these elements are less of a foctor. To test this hypothesis, in o compoign entitled "Seot Belts Poy Off," vehicles were stopped at random at sofe ploces out of traffic, and belted occuponts were given a modest prize (such os a free meal) donated by locol businesses and other orgonizotions. Each winner wos also given an entry blonk for o $500 monthly drowing and a $1000 grond prize. Television ond rodio spots were aired doily, ond newspoper coveroge included editoriol support for efforts to induce belt weoring.

About 50,000 copies of o brochure procloiming the importance of seat belt use and the "Seot Belts Poy Off" campoign were distributed in the community. Further, the compoign received the endorsement of the University and the two town governments as well os several civic orgonizations.

Boseline dato were collected at 17 mojor traffic locotions with about o 24% weoring rote observed, obout twice the national overage. Observers collected experimental doto on o weekly basis using o seven-level, stratified somple design. Observers beside the rood counted shoulder belt use in passenger cars having heod restraints. (Cars too old to hove heod restroints ore very unlikely to hove shoulder belts.) Since some drivers still wear lop belts only, our figures underestimate somewhot the octuol number restroined. We did not count utility vehicles, pickup trucks, or vons for data collection purposes, becouse many of these vehicles do not hove shoulder belts. However, for purposes of giving out incentives, oll of these vehicles closses were included (since only the lop belt need be worn to win o prize).

During the six month compoign we observed on overage weekly belt use increose from 24% boseline to 41% in the finol week. Weoring rates omang women were o bit higher than omang men — obout 2 percentage points. The weoring rote omong whites was obout fourfold higher thon among non-whites, o most serious finding in regord to factors involved in obtoining true community-wide success. Even six months ofter the end of the compoign, belt use is still 36-39%.

The obsence of seot belts ronks with drunk drivers os one of the two factors ossociated with the most highwoy deoths. Progress in controlling drunk drivers is very expensive ond olso rother uncertoin because of trying to control the deviant behovior of mony drivers for whom olcohol is o significant medical/behoviorol problem. In controst, increasing use of seat belts is a motter of inducing o narmol behovior omong members of the mainstreom populotion. In view of this, it is cleor that success in increosing belt use will have high payoff ot minimum cost.

Troffic croshes are the leoding couse of death for oge groups under 34 years old. Yes, the leoding couse, oheod of all other causes. For those over 34, croshes ore still a mojor cause of deoth. We moy dismiss those stotistics becouse riding in a cor feels so sofe. And thot's right. Trip by trip it is pretty sofe, but in yeors of driving the chonces of o serious crosh are great. Buckling up when you ride is





Belted occupants of randomly stopped cars received educational materials, a small prize (or coupon for a prize) and a chance in cash drawings.

the single mast effective thing yau can da ta increase yaur chances af escaping seriaus injury or death in a crash. Belts can save 200 of every 300 naw dying unbelted and can reduce seriaus injuries taa. That can translate into hundreds af lives saved each year in North Caralina. Nat wearing seat belts results in as many highway deaths as drunk drivers cause.

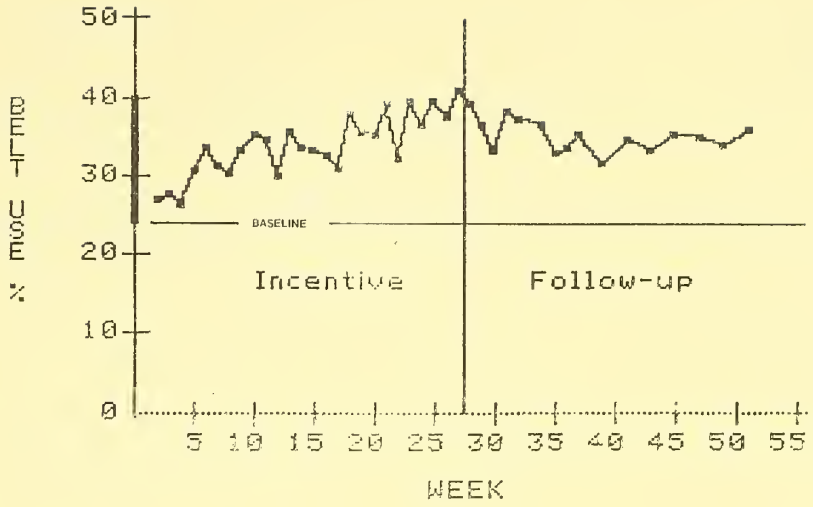
The bad news is that in the U. S. anly abaut 10% af peaple buckle up. Why sa law? Peaple give lats af excuses far nat wearing belts, same based an dangeraus myths.

"It's better ta be thrawn clear af the car."

NO, in fact it is many times worse. "Thrawn clear of the car" aften means being thrawn thraugh broken glass, anta the pavement, ar inta the path af anather car.

"My car might catch an fire and I'd be trapped."

NO, adds are thousands to one it wan't catch fire. *AND*, if quick escape is necessary, yau are mare likely to be canscious and able ta get aut af the car if you are wearing your seat belt. Maybe the main reason we don't wear belts is that we just don't think abaut it. Why nat start your community thinking abaut it. Start yaur own cammunity praject. It warked in Chapel Hill. Cantact yaur lacal police and civic leaders. Additianal infarmatian may be abtained by cantacting the University af North Carolina Highway Safety Research Center.



Belt use increased steadily during the incentive campaign, reaching 41% the final week. Once the contest ended, belt use slipped but stayed at 36% — a substantial net gain involving several thousand drivers.

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Canker Sores, Aphthous Ulcers, Mouth Ulcers

Claude S. Burton, M.D., Russell W. Eyre, M.D., and J. Lamar Callaway, M.D.

We may nat all use the same name far mouth ulcers but we all agree mauth ulcers are terribly painful. Hippacrates called mauth ulcers Aphthae and the term has remained in medical jargan. For thase unfartunate enaugh ta experience repeated attacks, mauth ulcers are a disaster. During an attack a persan is aften unable ta eat, drink, ar even talk. The pain may be severe enough ta interfere with sleep and is always bad enaugh ta affect ane's dispasitian. Many peaple have cansulted us aver the years far advice and we would like ta share aur experience with all wha are interested.

Canservative estimates suggest that at least 20% af the American papulatian will be affected, usually by the age of thirty. Attacks are aften precipitated by trauma (biting the tongue ar cheek, dental work, etc.) and in many wamen a striking assaciatian with menstrual periads has been nated. Allergy ta variaus faads appears to be respansible in same

cases and many potients believe stress is o foctor. Certoinly hoving o crap of ulcers is o stressful situation!

The ulcers are found throughout the mouth. Clinicol feotures moy be divided into four stoges but keep in mind thot not oll patients are typicol. During the first stage there is usuolly poin or tingling in the mouth though the mouth looks normal. In about 24 hours the preulcerative stoge (stage II) begins with the oppeoronce of a red bump ot the site af eorlier symptoms. 18-72 hours loter the third stage begins os the surface of the bump is sloughed, forming on ulcer ar small crater in the mouth. The ulcer is often exquisitely poinful, even to the slightest touch, ond moy be equally sensitive to the presence of faads and liquids. At this stoge the movement of the tongue during tolking may be so painful thot conversotion is avoided entirely. The ulcer stoge lasts from 1-16 doys until the ulcer is covered by a gray or yellowish membrone. Shortly ofter the membrane appeors, the pain obruptly ceases ond the healing stage (stoge IV) begins. The ulcers usuolly heol without scorring within two weeks. With deeper ulcers there moy be scorring. As indicoted obove, the time course is highly varioble ond the disappeoronce of poin rother obrupt. This voriobility confounds the study of vorious theropeutic strotegies.

In most coses the couse is unknown ond despite the most complete of investigotions the couse will not be discovered. Doctors call such coses "idiopathic" which is medicol jorgon for "I hove no idea whot is cousing this" or, jokingly, "the doctar is the idiot, the potient hos the pathology." More importontly, the term idiopathic implies thot the doctor has considered the known couses of the problem ond carefully excluded them on the basis of informotian gleoned from the history, physical exominotion, and in some coses, labarotory investigotian. A number of known causes of mouth ulcers must be considered, porticulorly in people with recurrent ottocks.

Occosionolly mouth ulcers indicate on underlying disease. Deficiencies of iron, folate, and vitomin B12 hove all been ossociated with mouth ulcers and where such deficiencies were identified, potients hove responded well to replocement theropy. Since iron, folote, ond B12 are essential for the formation of blood, one can easily assess body stores of these substonces by looking ot o somple of blaad under the microscope. For definitive diagnosis, o specimen of bone morrow may be exomined under the microscope or levels of these vitomins in blood moy be measured. If still in doubt, a theropeutic trial with these agents may be worronted.

Severol diseoses of the bowel ore associoted with mouth ulcers including ulcerotive colitis, regionol enteritis, and gluten sensitive enteropothy. A discussion of these diseoses is beyond the scope of this orticle. However, if symptoms such os diarrheo, weight loss, abdominol poin, and anemio ore ossocioted with mouth ulcers, these diognoses must be cansidered. Gluten sensitive enteropothy (GSE) is on illness reloted to a wheot ollergy. Severol patients with GSE and mouth ulcers without bowel symptoms hove been reported. In these coses o wheot-free diet has been helpful.

When genital ulcers ond mouth ulcers are both present on illness known os Behcet's syndrome must be excluded. Behcet's syndrome is ossocioted with poins in the joints, inflommotion in the veins leoding to thrombophlebitis, ond rore more serious complicotions. Of porticulor concern is o destructive eye diseose ossociated with Behcet's syndrome. Where this diognosis is considered we recommend ophtholmologicol consultotion.

The vast mojority of coses remoin unresolved. Cultures for bocteriol or viral ogents hove generolly been negotive leaving the impression thot aphthoe were not reloted ta infection. These eorly studies may have thrown investigotors off the trock since new, more sensitive techniques naw suggest that o virus moy be responsible for cousing the diseose. A recent study demonstroted the presence of herpes virus products in biopsy specimens of mouth ulcers despite the foct that virol cultures were negotive. The outhors of the study suggest thot the host response to the virus leods to ulceration.

If there were o cure, I doubt there would be sufficient interest to justify this orticle. Unfortunotely there is not. If the evidence for a virol couse is further substantioted then perhops voccinations or the newer antiviral drugs will hove a dromotic impoct on this diseose. Pending such an odvonce, the following approach will be helpful. After excluding the obove causes we osk potients with recurrent mouth ulcers ta keep o diory in the hapes of ferreting out that rore individual with o clearcut allergic couse. If every time o person eots peonuts he or she gets ulcers, then the cure is obvious.

Topicol onesthetics such os viscous xylocoine will relieve pain ond ollow eating and talking but must be used with certain coutions. If the onesthetic spreods to the throot then the gog reflex that protects us from choking moy be last with potentiolly dongerous consequences. A medicated mouthwash containing o mixture of steroid, tetracycline, ond the ontihistomine diphenhydromine (Benadryl), is useful in mony coses. Prednisone toblets ore often dromoticolly effective. Though prednisone toblets hove innumeroble side effects if they are token continuolly, the short term treatment of ophthoe rorely if ever causes ony difficulty. We advise select patients to toke 1 mg/kg ot the first sign of trouble ond for two doys thereofter. On this regimen mony ottocks never get off the ground. Topicol steraids ore an olternative but are difficult to use inside the mouth. Interestingly, like warts (which ore known to be caused by virus), hundreds of folk remedies are onecdotally effective. One of us has o sister who sweors by o tiny Ponomonian pebble corried just inside the cheek!

Activities of the North Carolina Committee on Trauma of the American College of Surgeons

Robert W. Youngblood, M.D.

• *The Committee on Trauma aims ultimately at preventing serious accidents. It sponsors a training program for doctors and nurses on acute care of traumatized patients and also collects data on the epidemiology of trauma.*

TRAUMA is the leading cause of death in the United States in the first four decades of life. It is exceeded only by heart disease and cancer in number of deaths in the entire population of the United States. The peak incidence of trauma deaths and disability is between the ages of fifteen and twenty-four. Thus, trauma affects our young, most productive citizens, causing death, disability and loss of productivity exceeding an estimated seventy-five million dollars per day. Approximately fifty percent of trauma deaths are caused by motor vehicle accidents, and all too frequently alcohol and drugs are significant contributing factors to the accident. Approximately twelve percent of the hospital beds in the United States are occupied by victims of injury. The primary efforts of the Committee on Trauma of the American College of Surgeons is to foster the optimal care of the traumatized patient.

The ultimate goal in the management of trauma is prevention. However, once an injury has occurred, optimal care consists of the re-establishment of normal physiologic processes in the most expeditious manner, with the least threat to life and without permanent disability. This consists of stabilization of the patient with management of his airway, treatment of shock, stabilization of fractures in the field and rapid transportation to a facility competent to manage his injuries. Included in such a system is a trained paramedical team for field stabilization and transportation, a communications system to alert the treatment facility and an organized and trained team to manage the patient expeditiously following his arrival at that facility.

The North Carolina Committee on Trauma of the American College of Surgeons has worked closely with the Office of Emergency Medical Services in an effort to obtain the best care for the trauma patient. Since 1981 this Committee has sponsored a training program, Advanced Trauma Life-Support (ATLS), in an effort to train physicians and nurses in the resuscitation and initial treatment of the injured. This is an intensive two day course consisting of a series of ten lectures, skill stations, animal laboratory, case studies and initial assessment of moulage patients. The student/faculty ratio is approximately three to one. In the past three years twenty-six such courses have been held for medical providers in North Carolina. This included two courses for medical students and three courses for surgical housestaff at teaching institutions. Additionally, three courses to train ATLS instructors have been given. A total of 58 instructors and 449 providers have been trained. Because of a strong belief in the team concept in the management of trauma, emergency room and critical care nurse courses have been given in conjunction with some of the physicians' courses to train nursing personnel in Advanced Trauma Life-Support. The thrust of this training is to establish a system of prioritization and to teach techniques for recognizing and managing life threatening and potentially disabling conditions. Such an intensive training program for those who are in the front lines of emergency care should result in a further lowering of mortality and morbidity for the injured.

On a time scale the first peak of trauma mortality is within a few minutes of the injury. This usually involves those individuals who have suffered brain laceration, a high cervical cord injury or major disruption of the heart or great vessels. These persons generally die at the scene of the accident and very little can be done in injuries of this magnitude which cause such rapid demise. The second peak of deaths on a time scale occur in those patients with severe injuries which rapidly progress to disrupt vital physiologic functions. Such injuries are expanding intracranial hematomas, airway obstruction, flail chest, sucking wounds of the chest, pericardial tamponade and bleeding from ruptured viscus or from major vessels. These patients may die within minutes to hours following their injuries but are salvageable if an efficient system of trauma management is available. It is these patients to whom the advanced trauma life-support training is directed.

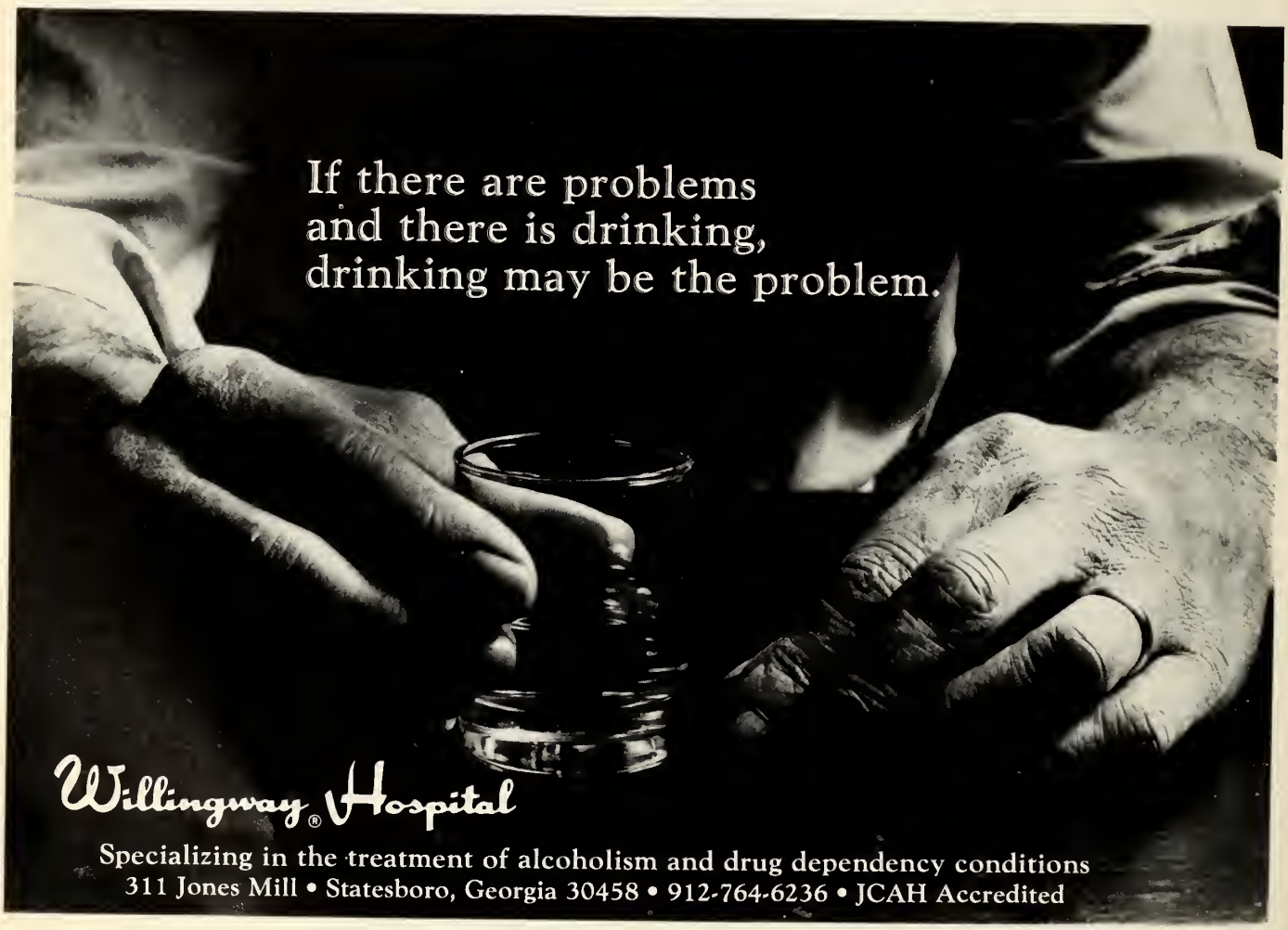
A second major area of interest of the N. C. Committee on Trauma is the epidemiology of trauma. Presently, there are few hard data on the incidence or severity of trauma in North Carolina. Stemming from the impetus of the N. C. Committee on Trauma, a study is presently being completed to evaluate the incidence of severe trauma and burns so that statistics might be available in planning the number of trauma centers necessary to serve citizens of North Carolina. This study has shown that an estimated 3,500

From Wilson Clinic P.A., Wilson 27893.

patients annually are severely injured. The North Carolina Committee on Trauma is seeking to establish a Trauma Registry so that prospective statistics may be obtained, not only for the incidence of injury, but for the outcome of these patients to establish trends and to outline the ideal management of the injured.

At one time the objective of the trauma surgeon was to "do no further harm." The time has come when we must look toward this dictum as being obsolete and strive for a system where, once the initial damage of the patient's trauma has been completed, that person can look toward a course of continuing improvement with recognition of his injuries, management of the life threatening situations and a continual improvement with lessening of risk of mortality and disability from the time he first finds paramedical assistance through his treatment and complete rehabilitation.

The ideal in trauma management is prevention. With the active support of the N. C. Committee on Trauma, the State of North Carolina is seeking to do this with legislation to try to rid our highways of those who are driving while impaired. We hope to lessen the severity of injuries with the use of seatbelts, as well as helmets for motorcyclists. When prevention fails and major injury occurs, we are attempting to establish a system of field stabilization with trained paramedical personnel, expeditious transportation to a facility capable of managing the patient's injuries and a communications system which allows for emergency department alert to anticipate the needs of the trauma victim. We, as physicians, have a duty to the citizens of North Carolina to foster prevention, to establish an expert emergency medical system, to equip our hospitals and to train ourselves to seek the optimal care of the injured.



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EDITORIAL

The University of North Carolina — North Carolina Memorial Hospital Statewide Trauma Center: How to Make Bricks Without Straw

H. J. Proctor, M.D.

"And Pharaoh commanded the same day the taskmasters of the people, and their officers, saying, Ye shall no more give the people straw to make brick, as heretofore: Let them go and gather straw for themselves. And the tale of the bricks, which they did make heretofore, ye shall lay upon them; ye shall not diminish ought thereof:"

Exodus 5:6

THE North Carolina Memorial Hospital is the major teaching hospital of the University of North Carolina School of Medicine and has, since its opening, served as a major referral center as well as a primary care resource for the area immediately surrounding Chapel Hill. As the population of North Carolina increased along with the speed limit, the popularity of alcohol and drugs, and a fondness for firearms, the number of trauma victims increased. In response to this increase in trauma admissions and to provide better patient care and better resident and medical student education, the University of North Carolina and the North Carolina Memorial Hospital became a self-proclaimed trauma center in 1972. Similar pressures brought about the creation of trauma services at Duke University Medical Center and the North Carolina Baptist Hospital.

An estimated 7,000 individuals per year are injured or burned in North Carolina badly enough to require hospitalization; nearly half of them have a trauma score of 12 or less indicating the desirability of admission to a major trauma center.[1] At the same time these data were becoming available, a requirement of the federal Emergency Medical Service Systems Act was the formal designation of trauma centers. Three level I or statewide trauma centers were designated, the North Carolina Memorial Hospital, Duke University Medical Center, and the North Carolina Baptist Hospital.

Although on a given day in the hands of a given surgeon any hospital can provide excellent care for the traumatized patient, what differentiates a trauma center from a nontrauma center is uniformity of a given capability (prescribed as part of the designation process) 24 hours per day, seven days per week. Perhaps the major determinant that sets the trauma center apart is an institution wide, multidisciplinary commitment to trauma care.

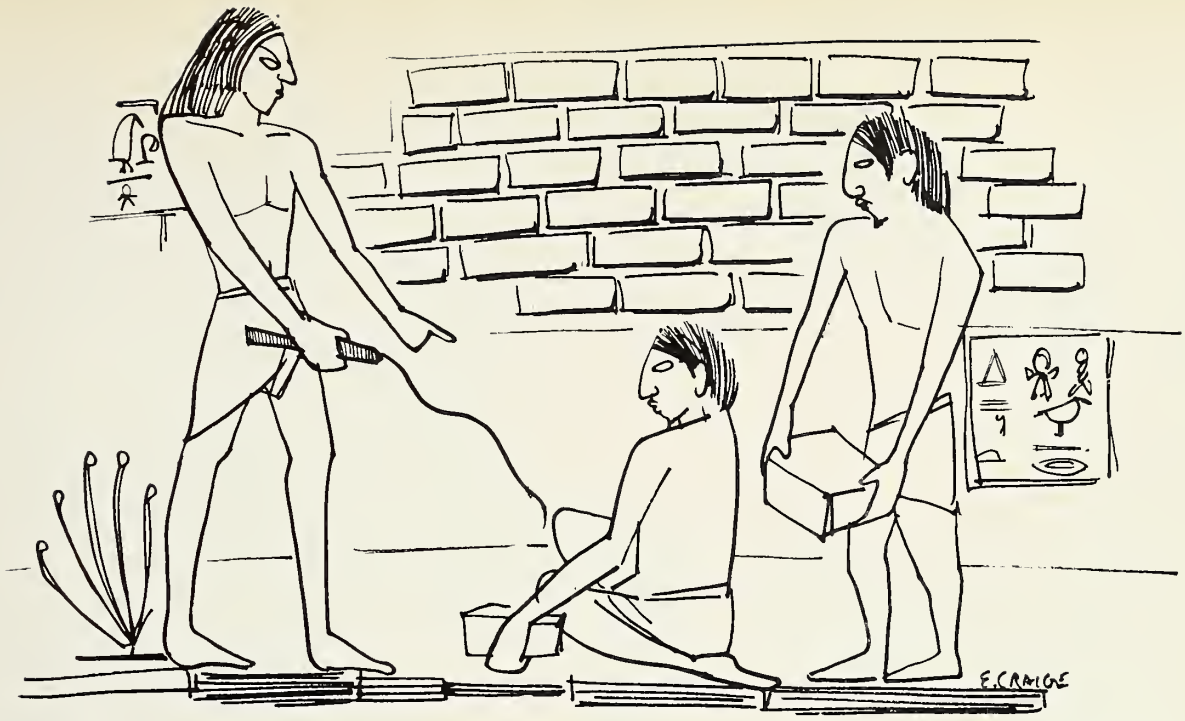
Specialized care for the seriously injured patient no longer begins or ends in the emergency room. It is an increasingly complex, continuing process requiring the coordinated efforts of professionals in many fields. The University of North Carolina — North Carolina Memorial Hospital Statewide Trauma Center was established to provide such care. The proficiency of the Center extends to emergency medical services, acute care, transportation, communications, rehabilitation, research, epidemiology, education and highway safety engineering, areas neither possible nor economically reasonable in a small hospital. Thus, statewide centers must by definition be located in large hospitals.

From the Trauma Section, Department of Surgery, University of North Carolina, Chapel Hill 27514.

Providing definitive care for individual victims of trauma is the sole function of the trauma service at Memorial Hospital. It is staffed by five general and thoracic surgeons. A chief resident, two assistant residents, medical students and surgeon's assistants are assigned to the service on a rotating basis. The staff is assisted by consultants from all the surgical disciplines and the departments of medicine, pediatrics and anesthesiology. The hospital's laboratories and radiological departments provide around-the-clock emergency support. Patients arriving at the hospital's Emergency Department are screened by the trauma team. Following stabilization and diagnosis, many patients are taken directly to surgery. The trauma service has priority access to an operating room equipped to permit measurements of such critical factors as cardiac output, pulmonary artery pressure, blood gases and pulmonary function. All patients with life-threatening injuries involving multiple organ systems are admitted to the 15-bed unit operated by the trauma service. The most critically injured and those voluntarily participating in research studies may be admitted to the Trauma Research Unit. Some patients who enter the trauma service are transferred to an appropriate specialty service after their conditions have been stabilized. There are in house at all times a fourth year surgical resident assisted by junior residents, with an attending surgeon in-house until midnight and all night on Saturday night. The Emergency Department is the physical link between the Trauma Center and the local and statewide Emergency Medical Service System. Radio communication permits physician supervision of emergency medical technicians serving in surrounding counties, as well as long-range communications with helicopters transporting patients to the hospital. Six physicians, three to five nurses and a variety of associated personnel are on duty in the Emergency Department at all times. Special areas are equipped to permit such complex resuscitation procedures as craniotomies and thoracotomies, in addition to the usual emergency services.

The North Carolina Jaycee Burn Center, a regional center for burn treatment, is located at Memorial Hospital. The 23-bed Burn Center offers the most advanced and effective methods of treatment for badly burned patients referred from hospitals throughout the state. The staff of the Burn Unit is experienced in dealing with the unique problems of resuscitation, recovery and rehabilitation presented by burn victims, and their efforts are supported by an aggressive program of burn injury research.

Critically injured patients who need the services of the trauma center may be flown to Memorial Hospital by helicopter. This service is provided by the Military Assistance



to Safety and Traffic (MAST) program, a joint federal-state service. The civilian head of this program is located in Chapel Hill. The MAST Program utilizes Army helicopters and flight crews from Ft. Bragg. Together with Marine and Coast Guard rescue flights, the MAST program flies about 200 missions a year to Memorial Hospital, landing at the helistop near the hospital's Emergency Department.

The rehabilitation program at the statewide center helps patients achieve full recovery by offering an intensive plan of physical retraining, psycho-social counseling and vocational counseling. Physical and occupational therapy are frequently initiated in the acute phase of trauma care. A team of physical therapists evaluates each patient's needs and designs an appropriate treatment program to maintain and increase strength, mobility and coordination. Treatments may include hydrotherapy and electrotherapy, as well as exercise programs. Occupational therapists help the patient achieve maximum independence and productivity, both during and after the recovery process, through exercise and treatment programs. They also provide splinting and positioning devices that prevent joint deformity and loss of function.

Since a clear understanding of shock and improved care of traumatized patients will come as a result of scientific investigation, particularly at the cell level, the Laboratories of Shock and Cellular Metabolism were created as part of the trauma center. The laboratories operate the hospital's Trauma Research Unit as well as laboratories devoted to animal studies. Supported by grants from the National Institutes of Health and the military, the laboratories administer an annual research budget of about $200,000.

Almost 50 percent of admissions to the trauma service are related to highway accidents. The UNC Highway Safety Research Center, a component of the Statewide Center, was created to evaluate the state's existing highway safety programs, coordinate the training of persons involved in highway safety, and close the gap between knowledge gained through highway safety research and its use in saving lives. The activities of the Highway Safety Research Center include studies into highway engineering, motorcycle safety, driver improvement, school bus safety and law enforcement.

The Trauma Center staff conducts an extensive outreach program in addition to its educational activities within the medical center. Staff members regularly assist in the training of rescue squad personnel, and provide faculty for ATLS courses. An OEMS grant enables staff members to visit community hospitals for training sessions in resuscitation, transportation, and recognition of patients appropriate for referral.

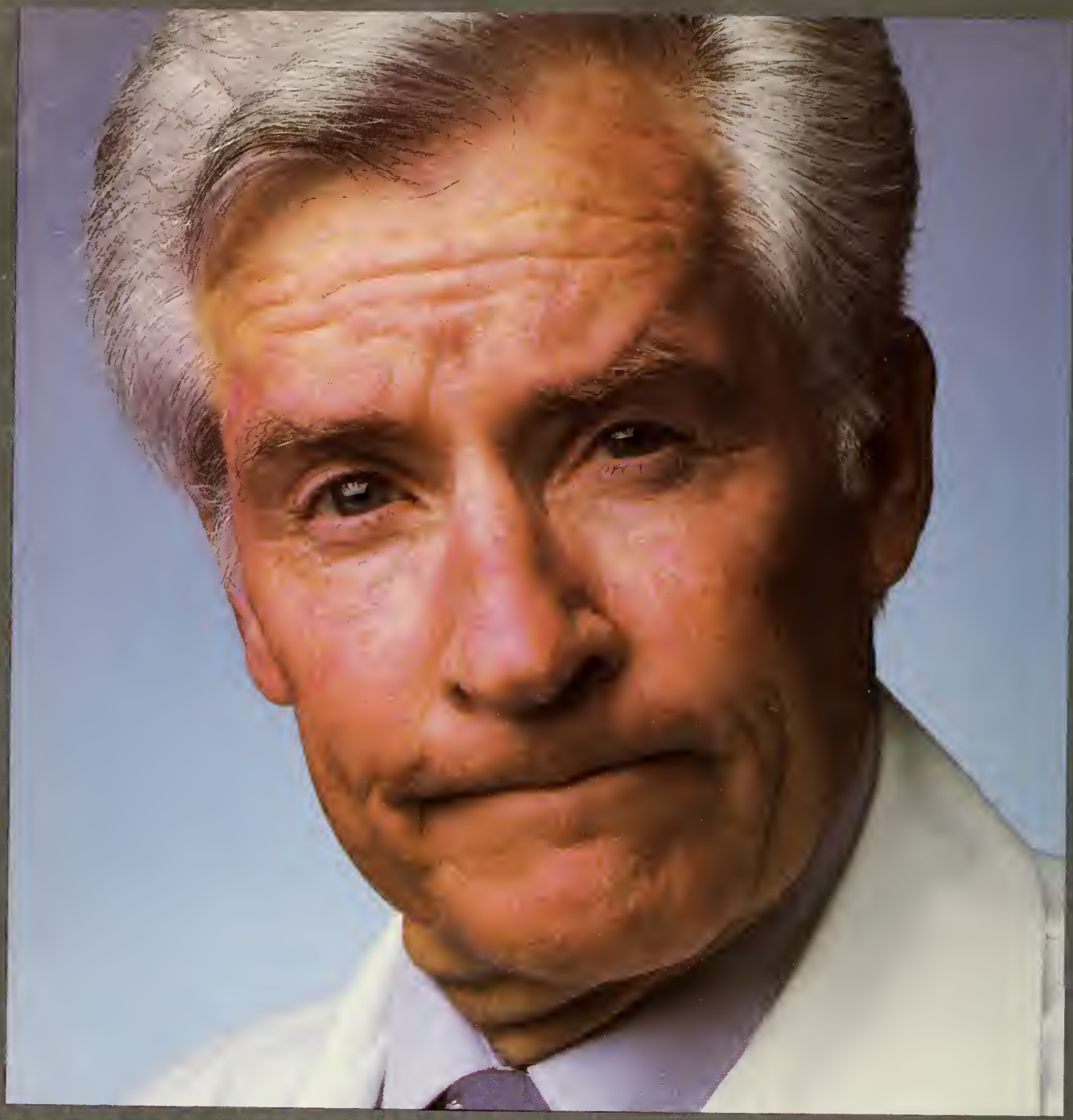
Many of the costs associated with maintaining the above capabilities are fixed, and depending on how they are computed are variously estimated at two to three million dollars a year. It obviously makes sense, not only for patient care but to reduce the cost per patient, to concentrate them all in one statewide center, or in as few centers as geography and transportation systems permit. The negative effect of this philosophy is that it concentrates the entire economic burden on a few hospitals, penalizing those who, in a sincere desire to improve patient care, hold themselves out as trauma centers. The collection rate of the trauma service at the University of North Carolina — North Carolina Memorial Hospital Statewide Center is 40%! Although automobile liability insurance is mandatory in North Carolina, delay in settlement of claims creates a cash flow problem stretching into years, while there is no coverage for the average gunshot wound. The impact of DRGs on transfer patterns is yet to be felt.

Who then will pay to operate an organized statewide trauma care system? The answer is not altogether clear, but it is the author's opinion that, like fire and police protection, if the citizens of North Carolina want access to top flight trauma care, it should be part of the tax burden. Such a tax could be imposed on all at a few dollars per capita, or distributed among the high users of the system as a surcharge on license plates, drivers' licenses, gasoline, etc.

As mentioned in the introductory comments to this editorial, North Carolinians can be justly proud of the progress made in trauma care. The consequence, however, has been the creation of a system which runs the risk of economic sanctions against the very hospitals best equipped to provide care, asking them, as did Pharaoh, to make bricks without straw.

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"To See a World In a Grain of Sand and a Heaven In a Wild Flower" — Oleander Poisoning

Ronald B. Mack, M.D.

• *The oleander – a fine plant to admire from afar.*

"HOLD Infinity In The Palm of Your Hand and Eternity In an Hour!!" These beautiful words of poetry you will immediately recognize as the opening lines of William Blake's *Auguries of Innocence*. Blake was the mystical English poet who died in 1827, not fully appreciated by the public for his artistic gifts (as none of us are). It is believed by some that he was the subtlest and most far reaching figure in the intellectual liberation of Europe that occurred at the end of the 18th Century.[1] (Leaping lizards, what does this have to do with toxicology?) In his references to innocence, he was thought to be talking about the imaginative separateness of the child. That is to say, his vision of innocence refers to the original state of happiness and spontaneous joy of childhood in which the imagination is totally free. This state can be achieved by adults as well.

Well, I am here to tell you that there is one "flower" that makes you "see heaven" in a hurry and it is the infamous *oleander,* AKA Nerium oleander. No question about it, this bit of flora is bad news; one leaf can kill an adult.

The oleander is a member of the dogbane family (that name dogbane should be a clue — plants in this family were used in the past to poison pesky, pesty, pets). This family contains in excess of 1,000 species of tropical trees, herbs, vines and shrubs and many of these species are very toxic, especially the Nerium oleander. In more remote historical times it was used as a protective substance to combat rodents and insects and was used as a remedy against malaria, leprosy, venereal disease (ouch!!), fever, as well as an abortifacient (watch your mouth, boy!!).

The oleander is quite pretty, but deadly, and is very popular as an ornamental shrub in our country's warmer climes: from Florida to California and in the Hawaiian Islands. In the more disagreeable, colder parts of the States it is grown as a house plant. How would you recognize this little darling without a name tag? I was reared in a concrete jungle and I couldn't identify it *with* a name tag. In any case, the shrub can be as tall as 20 feet. The leaves are unique and typically are a combination of simple, untoothed leaves produced in pairs. There is plenty of milky or gummy sap; the petals form a tube with a twisted appearance to the lobes. The fruit of the oleander is composed of one or two brown cigar or pencil shaped containers filled with myriads of small seeds.

The entire plant is potentially poisonous — the leaves, blossoms, twigs, sap, honey, seeds — all of it. This plant is so toxic — (how . . . toxic . . . is . . . it?) that if you put oleander in water, the water becomes poisonous; the smoke emanating from burning oleander is toxic; if you consume honey produced by bees who sucked the nectar from this fragrant evergreen you can be in big trouble, poison-wise. If you like to go camping, do not use an oleander branch as a meat or marshmallow skewer as you can die as a result of the toxin being transferred to the food. The oral lethal dose of oleander leaves in animals is approximately 0.5 mg per kilogram of body weight.

What does this plant contain that causes it to be so pernicious? The white and red flowering varieties contain at least five potent glycosides and at least 50 substances not yet identified. The major target organs of the toxins are the *cardiac* and *gastrointestinal* systems with death being caused by dysfunction of the heart. The cardiotoxic effects of oleander are probably due to the poisonous glycosides: *oleandrin, digitoxigenin* and *nerioside*. There are remarkable similarities in activity and chemical structure of these oleander glycosides and digitoxin (and of the foxglove plant). Many garden plants contain digitalis-like glycosides, e.g., the foxglove, of course, and lily of the valley and the star-of-Bethlehem. The oleander is thought to be more cardiotoxic than the foxglove.

If you happen to ingest oleander by accident or on purpose (it still is being used as a means of suicide) you immediately experience burning in the mouth — presumably due to the *saponins* in the plant. The saponins are quite irritating and are composed of various toxic surfactant glycosides. About one or two hours post ingestion the patient experiences *abdominal pain, nausea* and *vomiting, dizziness* and *bloody diarrhea* — an obviously miserable patient but hardly a specific syndrome. Later in the course of this devastating toxin (one to six hours) the patient experiences *bradycardia, drowsiness, loss of consciousness, hypotension, hypothermia, arrhythmias, dyspnea* and *death*. Morbidity and mortality seem to be related to the

cardiotoxicity of the oleander plant's glycosides which produce the arrhythmias and heart block and hyperkalemia. The bradycardia often progresses to A-V block and asystole. The ventricular arrhythmias that can ensue include PVCs, tachycardia and fibrillation and then exit — "to see heaven in a wild flower."

Many authorities believe that the major cardiac effects of oleander result from direct cardiotoxic action as well as central effects via the vagus nerve. The digitoxin-like oleander glycosides inhibit the ATP-ase dependent cation pump of the heart muscle, similar to digitalis. This same pump inhibition probably produces the elevation of the serum potassium often seen in these patients. Cardiac abnormalities can last 48 hours.

Two of the most interesting clinical features of oleander poisoning relate to the eyes; there is marked *pupillary dilatation* and there is a *distinct visual perceptive change* experienced by the patient: yellow and green colors are seen by the patient as well as geometric patterns around objects. This calls to mind the fascinating paper concerning the Dutch postimpressionist artist Vincent Van Gogh.[2] During the last years of this artist's tragic life his paintings contained many objects surrounded by halos and many, many objects painted yellow. The author of this paper hypothesizes that the artist was ingesting digitalis. Why digitalis? Apparently in the later part of the 19th Century this drug was used to combat epilepsy from which Van Gogh allegedly suffered.

The management of the patient who ingested this very toxic plant should involve gastric decontamination if the patient is seen early enough. Oleander produces vomiting in many patients soon after ingestion and that of course is to the patient's distinct advantage. In conscious patients ipecac syrup is usually indicated, otherwise lavage is the way to go. Activated charcoal and a saline cathartic should then be administered to further complete the gastrointestinal decontamination. Some current experts recommend administering charcoal and a saline cathartic every four hours until a charcoal colored stool is passed (Good heavens!!) indicating proper GI cleansing. Apparently, in the laboratory, there is cross reactivity of digoxin antibodies between oleander glycosides and digoxin in the radioimmunoassay for digoxin. Therefore, in a patient in whom you suspect oleander ingestion a digoxin concentration may confirm your suspicions if no other digitalis source has entered the patient's body.

Definite treatment for oleander poisoning should be the same as for digitalis poisoning. This involves monitoring serum potassium levels and monitoring cardiac rhythms of course. You could use atropine for bradycardia, lidocaine or propranolol for ventricular tachycardia, phenytoin for ventricular arrhythmias and electrical pacing for heart block. It is urged that propranolol not be utilized if the patient is undergoing bradycardia or second or third degree heart block. Theoretically neither diuresis nor extracorporeal removal modalities should work. To my knowledge cardiac glycoside specific antibodies (Fab fragments of sheep digoxin-specific antibodies) have not been used yet in oleander poisoning but just maybe someone will try it.

"Greens" seem to be a stable element of the Southern diet. To be honest, I never liked them. Now I figure I have a good excuse — who knows — they could be feeding me oleander!! Take no chances!!

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1. Kazin, A: *The Portable Blake*. New York, Viking Press, 1974.
2. Lee, TC: Van Gogh's vision. JAMA 1981, 245(7):727.

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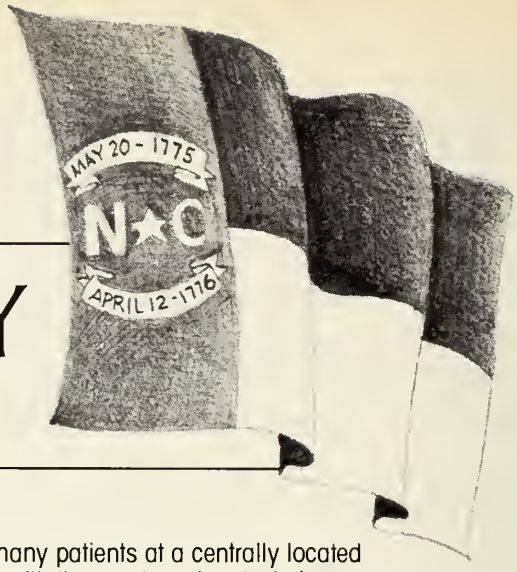
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On an average working day, Dr. Cannon rose at sunup to see patients at his converted-farmhouse clinic before setting out to make his usual 15 to 20 house calls around the countryside. Generally, after treating his primary patient, he saw each member of the family as well—his personal effort at preventive medicine.

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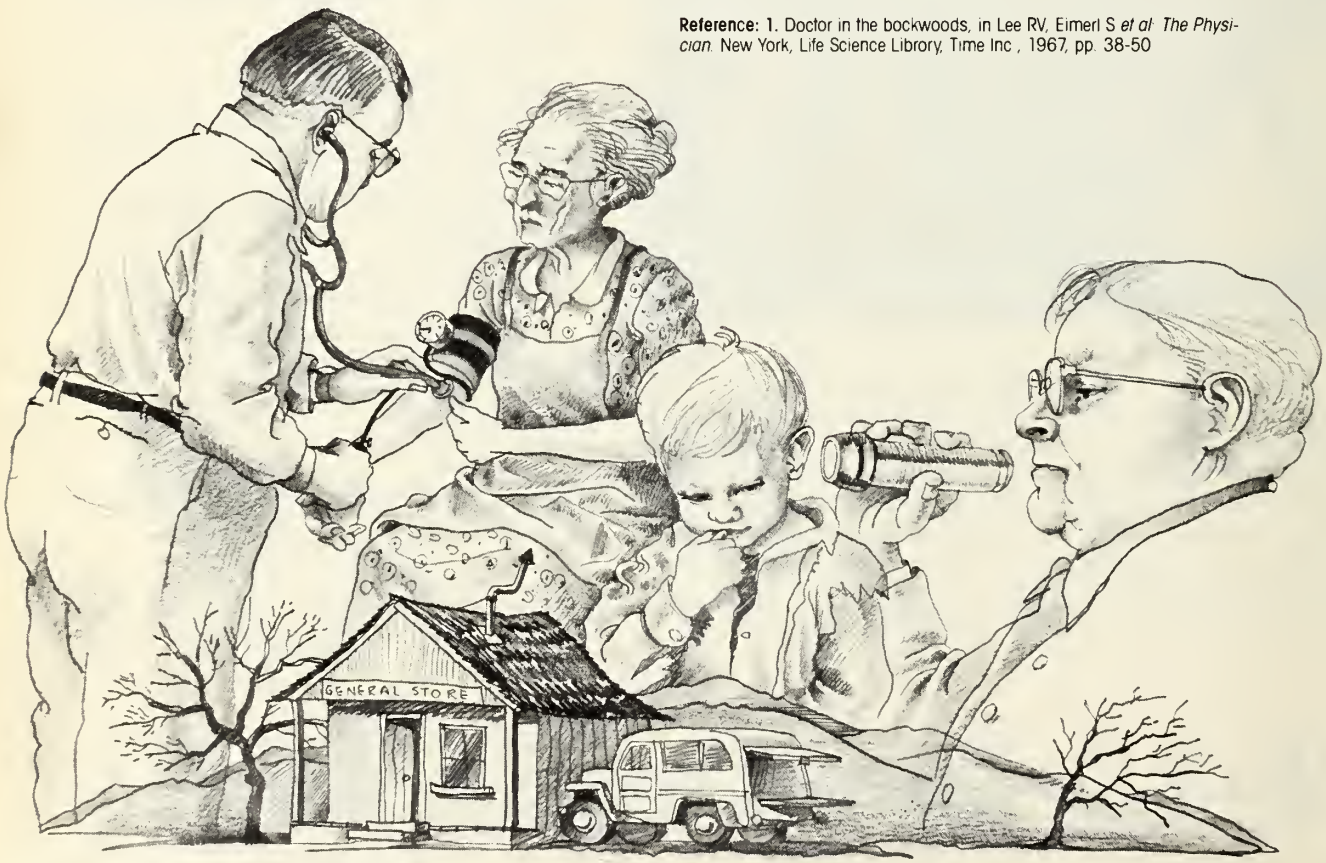
With the nearest hospital some 60 miles away and no pharmacy closer than an hour-and-a-half drive, Dr. Cannon filled his own prescriptions, delivered babies and treated many patients at a centrally located general store with the most modern techniques and medications. After a day on the road—usually within a 50-mile radius—Dr. Cannon's office hours would begin at 5:30 p.m. and stretch on until the last patient was attended to. His record-keeping sessions routinely filled the hour before midnight—rounding off Dr. Cannon's 18-hour day.

At all hours

But emergencies often interrupted his sleep. Dr. Cannon claimed his real office hours were 24 hours a day, and his patients revered him for it.

Dr. Cannon died in 1966 at the age of 68. He will be long remembered—most especially by the more than 5000 North Carolinians he helped bring into the world, some of them at the side of a rutted country road.

Reference: 1. Doctor in the backwoods, in Lee RV, Eimerl S *et al: The Physician.* New York, Life Science Library, Time Inc , 1967, pp. 38-50



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When the history reveals mixed depression and anxiety...

For the estimated 70 percent of nonpsychotic depressed patients who are also anxious,[1] Limbitrol provides both amitriptyline, specific for symptoms of depression, and the effects of Librium® (chlordiazepoxide HCl/Roche), the tested and dependable anxiolytic. Limbitrol is, therefore, a better choice for these patients than dual agents that contain a phenothiazine, a class of antipsychotic drugs which has been associated with tardive dyskinesia.

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Limbitrol also has a rapid onset of action which may lead to greater patient compliance. In a multicenter study, patients taking Limbitrol experienced 62% of their overall improvement within the first week of therapy.[2]

In another multicenter study,[3] the following symptoms associated with anxious depression were significantly reduced during the first two weeks of therapy:

- ☐ Headache—79%
- ☐ Early insomnia—91%
  Middle insomnia—87%
  Late insomnia—89%
- ☐ Gastrointestinal upset—73%

In two multicenter studies, only 1.9% of Limbitrol patients experienced cardiovascular side effects.[3]

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness such as operating machinery or driving a car.

References: 1. Rickels K: Drug treatment of anxiety in *Psychopharmacology in the Practice of Medicine,* edited by Jorvik ME; New York, Appleton-Century-Crofts, 1977, p. 316. **2.** Feighner JP *et al: Psychopharmacology 61*: 217-229, Mar. 1979. **3.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

In moderate depression and anxiety

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see summary of product information on following page.

LIMBITROL® Tablets Ⓝ Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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Source of Hair in a Pilonidal Sinus

Louis deS. Shaffner, M.D.

• *Where the hair comes from, how to treat the abscess and how to prevent a recurrence.*

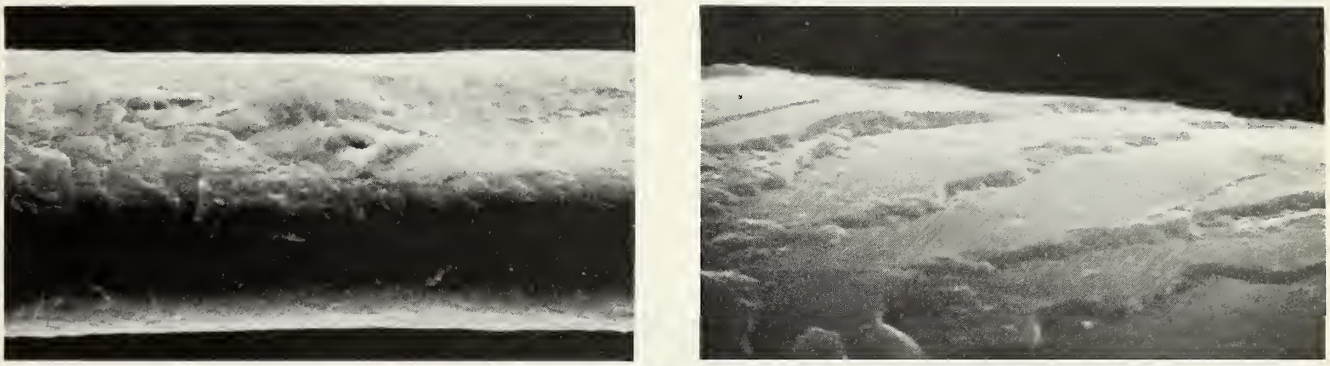


Figure 1: *Scanning electron microscopy of body hair shaft (left 520×; right 5200×). Root end is to the left.*

THE authors of recent articles on acute pilonidal sinus disease agree that it is an acquired infection secondary to hair in a pre-existing or *de novo* sinus in the intergluteal fold. There is still disagreement on how hair gets there. Current surgical textbooks postulate the "ingrowth" of hair; Raffman[1] suggests "implantion" by friction. Most authors agree that the hairs are always loose, and that they always lie with the root ends deep in the sinus. It is generally accepted that the sinuses do not contain hair follicles.

The scales on the hair shaft are like overlapping shingles from the root toward the tip (figure 1). Patey and Scarff[2] have postulated and Page[3] has demonstrated that the orientation of the scales is such that friction on the shaft between two skin surfaces, such as the nates, will cause the hair to migrate in the direction of the root end. This migration can be easily demonstrated by rubbing a hair longitudinally between the thumb and finger (figure 2). By that mechanism shed hairs can enter a pilonidal sinus.

In acute pilonidal sinus infection the abscess usually points to one side, but there is always at least one sinus opening in the midline (figure 3). It is through that opening that infection can start and hair shafts can migrate.

Adequate treatment, therefore, requires not only drainage of the abscess cavity, but also the removal of all midline pits or sinuses.[4] In an early case with only a small abscess,



Figure 2: *Stroking a hair longitudinally with thumb and finger will cause it to migrate toward the root end.*

From the Department of Surgery, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem 27103.



Figure 3: *Persistent midline pilonidal sinuses with recurrent infection after healing of previously drained abscess.*

this can all be done at one time under local anesthesia without hospital admission. Wide excisions of skin and the abscess wall are not necessary, but open packing for secondary healing is required. This could have been done in the case illustrated, thus obviating a second procedure.

Early skin bridging is prevented by weekly office treatments, and the hair is shaved as necessary until healing is complete in 4 to 6 weeks. After that the patient daily can remove loose hairs by stroking the area with the sticky side of a strip of adhesive tape folded over the finger tips.

For a patient with early irritation and visible hair shafts protruding from a small sinus, manual removal of the hair, sitz baths, and the daily use of adhesive tape may well forestall the development of an acute abscess.

References

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3. Page BH: The entry of hair into a pilonidal sinus. Br J Surg 1969;56:32.
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(BRIEF SUMMARY)

DESCRIPTION
Each tablet contains 200 mg meprobamate and 325 mg aspirin

INDICATIONS
Adjunct in short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone Effectiveness in long-term use, i e over 4 months, has not been assessed by systematic clinical studies Physicians should periodically reassess usefulness of drug for individual patients

CONTRAINDICATIONS
ASPIRIN Allergic or idiosyncratic reactions to aspirin or related compounds

MEPROBAMATE Acute intermittent porphyria allergic or idiosyncratic reactions to meprobamate or related compounds, e g carisoprodol, mebutamate, or carbromal

WARNINGS
ASPIRIN Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or those on anticoagulants In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes

MEPROBAMATE DRUG DEPENDENCE
Physical and psychological dependence, and abuse have occurred Chronic intoxication from prolonged ingestion of, usually, greater than recommended doses is manifested by ataxia, slurred speech, and vertigo Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms, e g anxiety, anorexia, or insomnia, or withdrawal reactions, e g , vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinosis, and, rarely, convulsive seizures Such seizures are more likely in persons with CNS damage or preexistent or latent convulsive disorders Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation, symptoms usually cease within next 12- to 48-hour period When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn

POTENTIALLY HAZARDOUS TASKS Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e g , driving or operating machinery

ADDITIVE EFFECTS Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously

USAGE IN PREGNANCY AND LACTATION
An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlordiezepoxide, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug

Meprobamate passes the placental barrier. It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in breast milk as compared to maternal plasma levels

USAGE IN CHILDREN Keep preparations with aspirin out of reach of children Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under

PRECAUTIONS
ASPIRIN Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics

MEPROBAMATE Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation Meprobamate is metabolized in the liver and excreted by the kidney, to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function Meprobamate occasionally may precipitate seizures in epileptic patients It should be prescribed cautiously and in small quantities to patients with suicidal tendencies

ADVERSE REACTIONS
ASPIRIN May cause epigastric discomfort, nausea, and vomiting Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur Patients receiving large doses of salicylates may develop tinnitus

MEPROBAMATE CNS Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity

GI Nausea, vomiting, diarrhea

CARDIOVASCULAR Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis

ALLERGIC OR IDIOSYNCRATIC Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin Other reactions include leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate/mebutamate and meprobamate/carbromal Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis Stevens-Johnson syndrome and bullous dermatitis have occurred

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC") Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura

OTHER Exacerbation of porphyric symptoms

DOSAGE AND ADMINISTRATION:
Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present Not recommended for patients 12 years of age and under

OVERDOSAGE:
Treatment is essentially symptomatic and supportive Any drug remaining in the stomach should be removed Induction of vomiting or gastric lavage may be indicated Activated charcoal may reduce absorption of both aspirin and meprobamate Aspirin overdosage produces usual symptoms and signs of salicylate intoxication Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole-blood transfusions Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse Some suicidal attempts have been fatal The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported Acute simple overdose (meprobamate alone) Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams

BLOOD LEVELS:
0 5-2 0 mg percent represents usual blood-level range of meprobamate after therapeutic doses The level may occasionally be as high as 3 0 mg percent

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdosage, such as stupor or light coma

10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment Some fatalities occur

At levels greater than 20 mg percent, more fatalities than survivals can be expected

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol) Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate Alkalinization of the urine increases excretion of salicylates Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption

HOW SUPPLIED:
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Colleen Gilbert

• *The first part of a two-part article on using ATG in immune-mediated diseases.*

ANTI-THYMOCYTE globulin (ATG) is an immunosuppressive agent of value in clinical renal transplantation and other investigational uses. It is commercially available from Upjohn as ATGAM sterile solution and has been approved for use in the management of renal allograft rejection since 1981.[1, 2] This agent is used for its lymphocyte-selective immunosuppressive actions in an array of immune-mediated disease states. ATG has been examined for use in organ transplantation rejection therapy,[3-14] aplastic anemia,[15-21] lymphomas and leukemias,[22, 23] graft-versus-host disease,[24-26] multiple sclerosis[27] and myasthenia gravis.[28, 29] The use of ATGAM remains controversial despite the established clinical benefits for some patients. In addition to ATGAM, there are other, non-FDA approved anti-lymphocyte globulin preparations available around the country. In particular, there have been extensive studies with an anti-sera produced at the University of Minnesota called Minnesota Anti-lymphoblast Globulin (MAG).[1, 30] In order to avoid confusion, the following discussion will be limited to clinical trials of ATGAM unless otherwise indicated.

Immunopharmacology

ATG is an equine, heterologous antibody prepared against human thymocytes.[2] This purified globulin is a potent immunosuppressive agent in animal models.[1] Therapeutic efficacy of ATG in humans has been controversial. The precise mechanism of its action is not yet known. A brief review of immunoglobulin structure and function, and of the human immune system, will aid in the understanding of ATG function, including adverse effects.[31, 32]

A schematic drawing of a monomeric IgG immunoglobulin is seen in figure 1. The Fab portion of the molecule binds to specific antigenic sites to form antigen-antibody complexes. These complexes may activate the complement cascade to cause complement-mediated cytotoxicity or they may be subsequently phagocytosed by macrophages or polymorphonuclear neutrophils. The Fc portion of the molecule is responsible for various biological activities of the antibody such as complement activation and the ability to cross the placenta. Many sub-populations of cells, such as B-cells, carry Fc-receptors on their surface which bind immunoglobulin and mediate further immune responses. The immune system consists of the integrated actions of T and B lymphocytes and macrophages. There are two functional components to the human immune system: cell-mediated immunity and humoral immunity. The cellular axis consists of T cells, macrophages and soluble lymphokines. Cellular immunity is activated by T-cell recognition of antigen. This results in release of various lymphokines and activation of macrophages. The macrophage is important in presentation of antigen to T and B cells as well as for its action as an effector cell to phagocytose foreign material. A subpopulation of T cells can be stimulated to proliferate and directly kill foreign cells. These effector T-cytotoxic cells are regulated by two other types of T cells known as suppressor and helper T cells. Helper T cells act as inducer cells to mediate both cellular and humoral immune response. They release soluble lymphokines such as T cell growth factor (TCGF). Suppressor T cells exist in a relatively fixed ratio to helper T cells and are important in the fine tuning of humoral and cell-mediated immune responses. The humoral axis of the immune system is re-

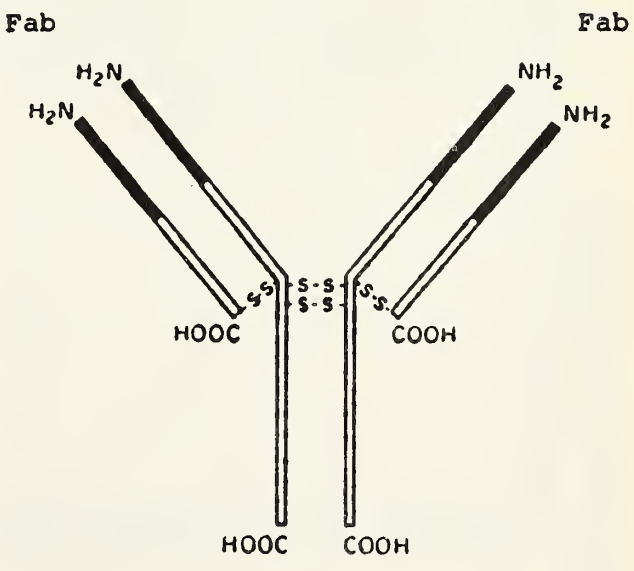


Figure 1.

From the Department of Pharmacy, Duke University Medical Center, Durham 27710.

sponsible for the production of antibody and is particularly essential to fight pyrogenic bacterial infections. The B cell has immunoglobulin as well as Fc receptors on its surface membrane. Antigens may directly bind the cell and stimulate immunoglobulin production (T-independent antibody) or T helper cells and macrophages may augment B cell response by antigen presentation (T-dependent antibody). Generally, foreign serum proteins are thymus dependent immunogens. Upon initial antigenic challenge, the B cells respond with a low titer of T-independent IgM antibody which appears in approximately ten days. Rechallenge of the humoral immunity results in a much higher titer of IgG antibody which is T-dependent and appears in three to five days. Continued boosting of the immune system by multiple exposure to antigen may result in a hyperimmune serum with high concentrations of IgG antibody. This is an important principle behind the production of anti-thymocyte globulin.

ATGAM is produced by immunizing horses with thymocytes obtained from thymus tissue removed during surgery.[33] Other sources of antigen which can be used are peripheral blood lymphocytes, lymphoblastoid cell lines and cadaveric splenic lymphocytes.[31] Species which may be used to prepare anti-lymphocyte sera include goat, rabbit and horse.[28, 31] ATGAM is prepared in horses due to the large volumes of plasma that can be obtained. The horses are injected with purified thymocytes every two weeks for three months. Equine plasma is drawn into sterile, heparinized bottles biweekly. The pooled equine plasma is then processed and purified monomeric IgG is isolated. This is then absorbed with human erythrocyte stroma and soluble human plasma proteins to remove cross-reactive antibodies to these substances. The final yield is 9-16 grams IgG protein per liter of plasma.[33]

There are many *in vitro* and *in vivo* assays used to assess the safety and potency of each ATG lot.[33] The rosette inhibition assay is used to qualitatively predict ATG potency. A titer of $\geq$ 1:5,000 is considered desirable. A T cell rosette is formed by the binding of sheep red blood cells to thymocyte surface membrane. Inhibition of rosetting indicates functional T cell damage by the ATG. Inhibition of T cell rosetting generally correlates with increased graft survival time in the Monkey Skin Graft Survival Assay.[33, 34] The skin grafts survive seven to 10 days without ATG and may be prolonged to over 30 days with ATG. However, clinical efficacy has not been proven to correlate with these assays. Reports have been conflicting and ATG lot variability remains a major concern with the use of ATGAM.

The precise mechanism of action of ATG has not been elucidated. In general, the immunosuppressive effect of ATG is due to binding to T cells and inhibition of good cell mediated immune response.[1, 2] A recent study by Thomas et al indicates that effective ATG is correlated with enhancement of non-specific suppressor cells.[34] Binding of T cells by ATG may cause actual thymocyte destruction by complement-mediated cytotoxicity or macrophage activation and phagocytosis. Alternatively, the ATG may inhibit cell membrane changes necessary for cytotoxic T cell activity or may neutralize lymphokines produced by the T cell. In any case, anti-thymocyte globulin clearly acts on the cell-mediated immune system and has minimal effect on the humoral immunity.

In clinical transplantation, the HLA/DR histocompatability antigens are responsible for organ rejection phenomena.[31, 32] The host recipient recognizes foreign surface antigens on the donor organ and mounts both a cell-mediated and a humoral immune response. Cytotoxic T effector cells are primarily responsible for acute cellular rejection episodes, and antibodies are responsible for acute humoral rejection. If donor and recipient are perfect HLA matches, as in identical twins, the allograft is much more likely to survive. Unfortunately, such perfect matches are rare and HLA antigen mediated rejection is a major problem in clinical transplantation. The presence of HLA-D/Dr sensitizing antigen causes stimulation of helper T cells. Proliferation of the helper cells can result in direct binding and lysis of HLA/Dr antigen bearing cells. In addition, these T helper cells amplify cytotoxic T cell response to the other HLA-A,B,C antigens and mediate B-cell production of antibodies to the incompatible HLA antigen bearing cells. ATG may act in this setting to bind T cells and inhibit helper and cytotoxic T cell function.[31] It may also prevent the production of soluble mediators by helper T cells and decrease the stimulatory effect of HLA-D/Dr antigens.[31]

Renal Allograft Rejection

Allograft rejection has historically been controlled by immunosuppressive therapy with azathioprine and corticosteroids. The azathioprine dose (3-5 mg/kg/day) is adjusted according to complete blood counts and steroid doses are tapered over weeks to months. This approach has resulted in approximately 50% graft survival at one year for cadaveric renal allografts.[31] Onset of acute rejection episodes is seen at 7 to 21 days post-transplantation. Symptoms include fever, chills, oliguria, and a swollen, tender graft.[31] ATGAM is approved for use in renal allograft recipients for the prevention and treatment of acute rejection episodes. Studies generally have looked at the effect of adding ATG to the current immunosuppressive regimen. These studies are difficult to evaluate and compare, due to ATGAM lot variability, poorly selected controls and dosage variability.[1]

A prospective, randomized trial of prophylactic ATG therapy in cadaveric renal allograft recipients was reported by Cosimi in 1981.[35] Control patients (n = 44) received standard azathioprine and corticosteroid immunosuppressive therapy, while the ATG study group (n = 60) received this regimen plus 14 days of ATGAM (10-30 mg/kg/day). Those patients receiving concomitant ATG experienced significantly fewer rejection episodes in the first 60 days after transplantation (56% vs 84%; $p<0.05$). There were equal numbers of serious infections in all patients and fewer cases of avascular necrosis of the bone in the ATG group. This may have been due to decreased steroid requirements in those patients.

Kountz et al looked at ATG dosage and graft survival in cadaveric renal transplantation.[6] Control patients (n = 21) received azathioprine (150 mg/day) and prednisone, low dose ATGAM patients (n = 30) received additional ATG-250 mg QD for 14 days, and high dose ATGAM patients (n = 22) received ATG 750 mg QD for 14 days. They found

no benefit to using low dose ATG but noted significant improvement in renal graft survival in patients receiving high dose ATG ($p<0.03$). Those patients showed delayed onset of first rejection episodes, lower total steroid dose and increased percentage of functional graft survival rates at 12 months.

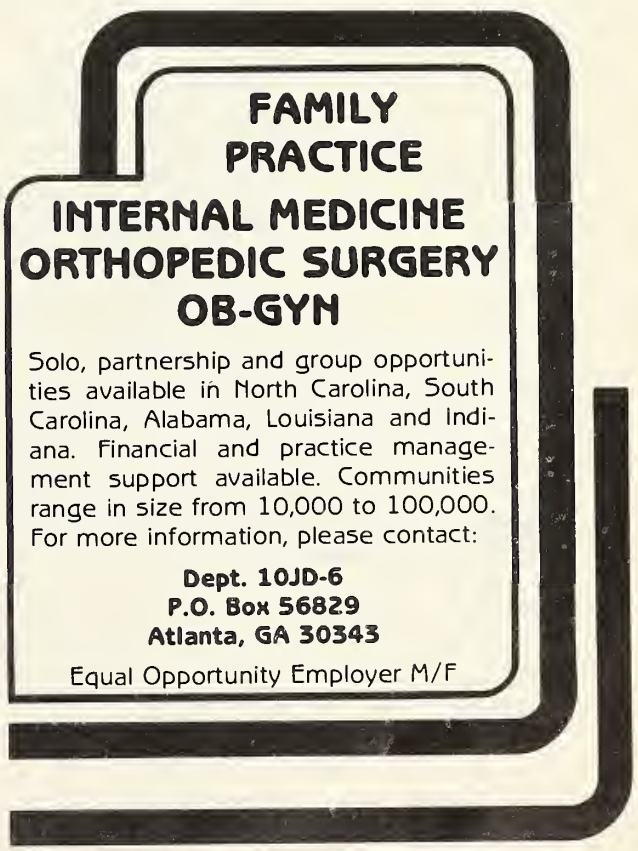
In another multicenter trial of a 14 dose ATG regimen, four different ATGAM lots were compared.[12] Wechter et al evaluated a total of 360 patients. All patients received standard immunosuppression with azathioprine and prednisone. Both living related and cadaveric renal allografts were included in the study. Those patients receiving additional ATG therapy were given an average dose of 20 mg/kg/day for 14 days. Results were variable, with only one of four ATGAM lots demonstrating significantly fewer rejection episodes in the first 28 days post-transplantation ($p\leq0.01$). Graft survival at 12 months slightly favored ATG but was not statistically significant for three of the lots. They also noted that steroid requirements were not significantly decreased at 28 days by the use of ATGAM. The rosette inhibition and monkey skin graft survival assays did not predict clinical efficacy of ATGAM lots in this trial.

Wechter et al went on to look at extended treatment with ATG in 20 cadaveric renal allograft patients.[13] These patients received azathioprine, prednisone plus ATGAM as follows; 7 mg/kg/day × 4 days, 3.5 mg/kg/day × 26 days, 7 mg/kg twice weekly × 8 weeks, and finally, 7 mg/kg once a week for the last 4 weeks. Control patients ($n = 20$) received the azathioprine and prednisone alone. Results of this regimen were much more encouraging. There were significantly fewer rejection episodes in the first 14 (25% vs 65%; $p<0.03$) and 28 (45% vs 85%; $p<0.02$) days and functional graft survival at 12 months (70% vs 35%) and 24 months (60% vs 35%) was improved in the ATG study group. ATGAM has been evaluated in several studies for reversal of established renal allograft rejection. Shield et al reported a prospective, randomized study of ATG in the treatment of rejection in recipients of living related donor renal allografts.[9] Patients were treated prophylactically with azathioprine and prednisone. When acute rejection episodes were documented patients were randomized to receive either ATG 15 mg/kg/day for 14 days then QOD for 14 days, or 1 g/day Solu-Medrol for 5 days followed by an oral prednisone taper. Results showed that ATG reversed rejection twice as fast as steroid therapy (3.1 vs 6.3 days). Although allograft survival was identical in the two groups, patients receiving ATG required significantly less total steroids in the first 60 days post-transplantation.

A similar study by Nowygrod et al compared ATGAM (15 mg/kg/day × 10 or 12 days) with methylprednisolone (15 mg/kg × 4 days then tapered) for reversal of renal allograft rejection.[8] Both regimens were essentially equivalent for treatment of rejection. However, the grafts lost in the ATG group (5/32) were documented (by biopsy) to be due to humoral rejection. They also noted improved allograft survival at 12 months and decreased mortality rate in patients receiving ATG. An important point of this study is that patients receiving the 10 day ATG regimen had more frequent second rejection episodes than those patients treated for 14-21 days.

Filo et al also evaluated therapy of acute renal allograft rejection with ATG.[16, 17] ATGAM (10 mg/kg × 15 days) was randomized versus methylprednisolone (30 day taper) to treat all rejection episodes in 79 patients who had received cadaveric or LRD kidneys. Patients receiving ATGAM for a first rejection episode responded more rapidly than patients treated with steroids ($p = .05$) and percent graft survival was higher with ATG ($p = .02$). However, subsequent rejection episodes treated with ATG or steroids reversed in an equal number of days and percent graft survival was also equal. Accumulated graft survival after three rejection episodes was better in the ATG groups, particularly in those LRD allograft recipients (79% vs 59%).

Part II will appear in the December 1984 issue of the NCMJ. References available from the NCMJ editorial office.



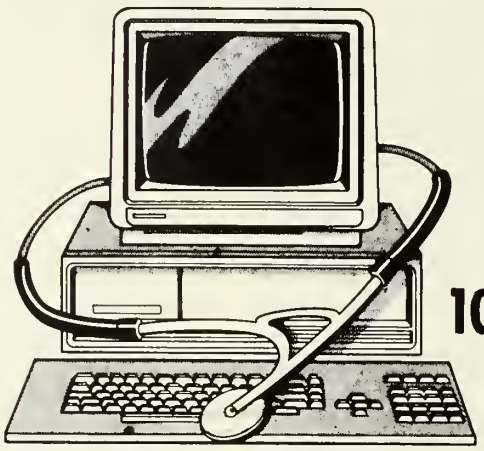


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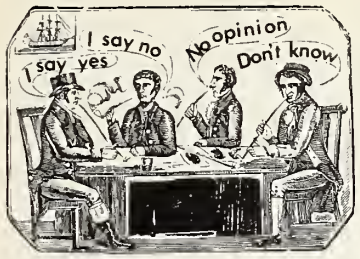
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Overlap Between Public Health and Private Physician

Eugene W. Linfors, M.D., editor

The question for November is: **What areas of the public health sector overlap with those of the personal physician? What areas should overlap?**

From Dr. Robert G. Brame, an obstetrician and gynecologist in Raleigh.

Public health departments provide health maintenance, prenatal care, contraception and diagnosis and treatment of sexually transmitted diseases to a segment of the population who do not have the financial resources to see a private, "personal" physician, although a small percentage of patients who take advantage of health department services are not medically indigent. The health department, for the most part, however, provides services to the indigent and until some other way to provide that service is devised, health departments will likely continue to serve as "primary physician" to many of our citizens.

From Dr. W. B. Bunn, an occupational medicine specialist in Durham.

Perhaps the only significant addition to the Hippocrates historical evaluation was added by Ramazzini in 1713. He stated, "when a doctor visits a working class home he should be content to sit on the three legged stool if there isn't a gilded chair and he should take time for his examination." To the questions recommended by Hippocrates add one more — What is your occupation?

Although it is estimated that at least 20% of all cancer cases are occupationally related and 3.2 million workers are disabled and 60.5 workdays are lost per one hundred workers, the occupational history is commonly missing from charts of both outpatients and inpatients. In a technological society where there are hundreds of thousands of chemical compounds used in industry, the toxic and carcinogenic effects of chemicals must be considered. Therefore it has become important that an occupational or environmental etiology be considered for all disease processes.

For example, in consultation I recently saw a patient with a peripheral neuropathy who had been evaluated by a general practitioner, an internist, and a neurologist. Although two of the physicians had asked the occupation of the patient and several possible exposures has been elicited, no formal occupational history had been taken. In this particular case the patient was manager of a print shop and had minimal exposure to chemicals in the usual course of employment. He had, however, recently misapplied a herbicide to weeds around his workplace without protective equipment. The onset of the disease process and the degree of exposure were consistent with an acute toxic neuropathy which was documented by clinical testing. The patient was withdrawn from further exposure and he regained full function.

Health care personnel often omit the occupational history because the exposures are unfamiliar to them or are regulated by occupational or environmental standards. The former is not acceptable practice and the latter assumption is not a valid one since only a small percentage of the hundreds of thousands of chemicals are regulated and most chemicals have not been tested for adverse effects. In addition, it is impossible to enforce governmental standards given the resources available.

Further, physicians often decide that a detailed occupational history and definition of an exact agent are unnecessary since the patient may have ceased exposure or can be withdrawn from exposure. This decision creates two problems. First, other workers are commonly exposed to the agent and may have a similar adverse effect. Prevention is the best solution for all disease processes and the reduction of occupational exposure to harmful agents is an excellent example. Second, the definition and clarification of the exposure will aid in determining the prognosis of the acute process and future risks. It may also allay the financial burden of treatment by alternate compensation systems designed for this purpose.

In conclusion, omission of the occupational health history from the history and physical works to the detriment of the patient and society. It is an important tool in patient care, preventive medicine, and assessment of future risks and responsibilities.

From Dr. Jesse B. Caldwell, Jr., a gynecologist in Gastonia.

One *could* ask, "what areas of a personal physician overlap with those of public health?," since there seems to

be evidence that public health came first. Recorded history indicates that quarantine and isolation were used in the time of Moses and Aaron in cases of leprosy. The Romans built sewers and baths to control disease.

In times since, public health services have encompassed wider areas of medicine. These have accelerated since the isolation of the tubercle bacillus just over a hundred years ago and the acceptance of the "germ theory of disease."

Today, the two sectors do overlap in many areas. While enumeration and identification would be interesting, it appears that such overlapping is a balancing act and not necessarily a competitive one even though some public health facilities are now charging for services such as immunizations, pap smears, etc.

Areas that should overlap would be those services which could be provided by a public health department to persons of limited means who would not otherwise use a personal physician. Also, instances are known when a patient with a condition, such as a venereal disease, prefers to visit a public health facility.

There seems to be little interest by physicians in the overlapping in areas of environmental health services, such as sanitary control of water supplies, sewage disposal, regulation of food distribution, and also the collection of vital statistics, etc.

From Dr. Martin J. Kreshon, an ophthalmologist from Charlotte.

Over the past twenty-three years I have been actively involved in the private practice of ophthalmology in the largest city in the Carolinas. In dealing with a very busy practice, I have found that there is an unquenchable thirst for medical knowledge existing in most of my patients. There has been a "communication gap" between the patient and his physician. All of us who have been blessed with the title "physician" need to be aware of these needs and make some attempt to communicate our knowledge to our patients.

Most of us have had some experience in giving informative medical talks at the PTA, industrial safety conferences, civic club luncheons or talk shows at the local radio or TV station. When an audience is asked to "open up" we are all amazed by the depth and number of intelligent questions posed for the physicians. Such exchanges can act as a two-way street reaping rewards to both participants.

Such is the case in the eye donor arena. Audiences want to know more about donation of eyes and having obtained this information, they are in a much better position to decide concerning a donor card. In approaching a family for possible donation of corneal tissue, I have found that knowledge concerning transplantation or a contact with a local Lions Club member who had discussed possible eye donor situations, has always been helpful in coming to some agreement concerning the use of the tissue. The "public sector" attitudes can be a tremendous help to any of us who find a need for communication which must be accomplished in a short period of time. Time spent in informative service to others will reap benefits for all types of physician-public relationships in the future.

From Dr. Nicholas E. Stratas, a psychiatrist in Raleigh

To speak of overlap is in some quarters touted as good, but it appears that a more pluralistic system may emphasize care for the middle class and continue to abandon the indigent. Mental health center (and proprietary system) proponents argue that a locally based and free market should improve mental health care. There is nothing in the research literature to explore how types of terms of patient-physician-institution contracts affect efficacy and quality of care or type of patients served. It seems clear that method of payment (fee-for-service, prepayment, public payment) will affect the contract and, therefore, the service delivery. Public mental health hospitalization (and lump sum prepayments) encourage staff to extend length of hospital stay. In addition, accountability, which is quite clear in the patient-physician relationship of the personal physician, is unclear in the public (and often in proprietary) systems and can be expected to produce economic and patient abuse. Nonprofit systems are five to seven times more likely to deliver unreimbursed or underreimbursed services than are private for-profit providers.

There are clearly overlapping inpatient systems of care — the state funded public state hospitals and mental health centers, the for-profit hospital chains and psychiatric units in general hospitals. There is also overlapping in the provision of outpatient services — the public mental health state/local government funded and the personal physician provided. Except for academic settings, the for-profit chains have not yet moved into outpatient services in North Carolina. Whether and what areas should overlap is a moot question. The quality of our system of care is predicated on the personal physician-patient contract. This model needs to be an integral part of any other system. The public mental health system should shift to a private sector, personal physician model and recognize its "third party" role in services for the indigent population with the population able to pay personally or through other third party coverage given the option to choose. Even in the institutional settings, public mental health and proprietary, the basic model needs to be the personal physician-patient contract. This needs to be established at first contact and stated clearly to include goals, initially evaluatory and diagnostic, then treatment planning integrating the patient goals, identifying the treatment modalities, the temporal needs and the cost and mode of payment. Public mental health facilities should explore the open staff, personal physician model. Public mental health services can provide medical assessment and care for the chronically mentally ill, with each patient having a personal physician responsible for his or her care. The public mental health system can provide the rehabilitative, socialization and domiciliary supports whether in a state hospital or local mental health setting.

The chronically mentally ill are extremely vulnerable as consumers of care because they frequently cannot make informed decisions. State government then becomes the actual consumer of care and should intercede for the chronic mentally ill, promote public information programs and foster personal physician involvement as service providers. A further problem with the chronic mentally ill is that only 10 percent live with their families, 15 percent in state

mental hospitals and 68 percent in nursing or boarding homes. Here as well the personal physician model needs to be strengthened.

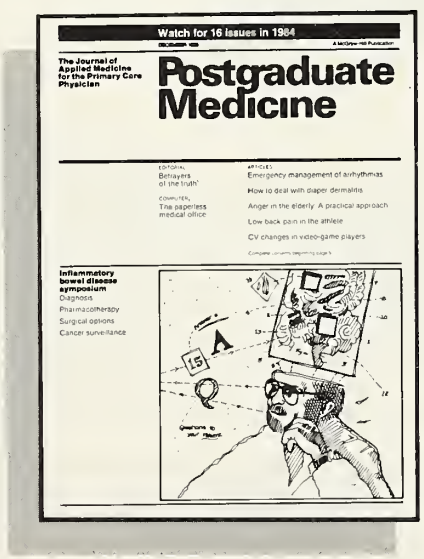
Finally, the public mental health and private systems need to overlap and work together to establish and monitor quality of care, improve third party coverage, reduce the stigma of mental illness and encourage research. The public mental health sector can continue research into the causes and treatment of mental illness and gather more accurate epidemiological data for analysis and insights.

• EDITOR'S NOTE: Thus it would seem that, among those kind enough to respond to the November question, there are no "turf" issues in the overlap between areas of the public health sector and those of the personal physician. Rather they seem to offer complementary services to our society or similar services to different segments of the society. It was suggested that public mental health care delivery should take more cognizance of the private physician model. Also, it was suggested that perhaps personal physicians should take a larger role in the area of public health, such as learning more about occupational and environmental standards for toxin exposure for the areas in which our patients work. If that's true, should we as health providers also be more concerned about other areas of public safety, e.g., seat belt usage, water and air quality, nuclear war, child or parent abuse? If so, what should we do about it?

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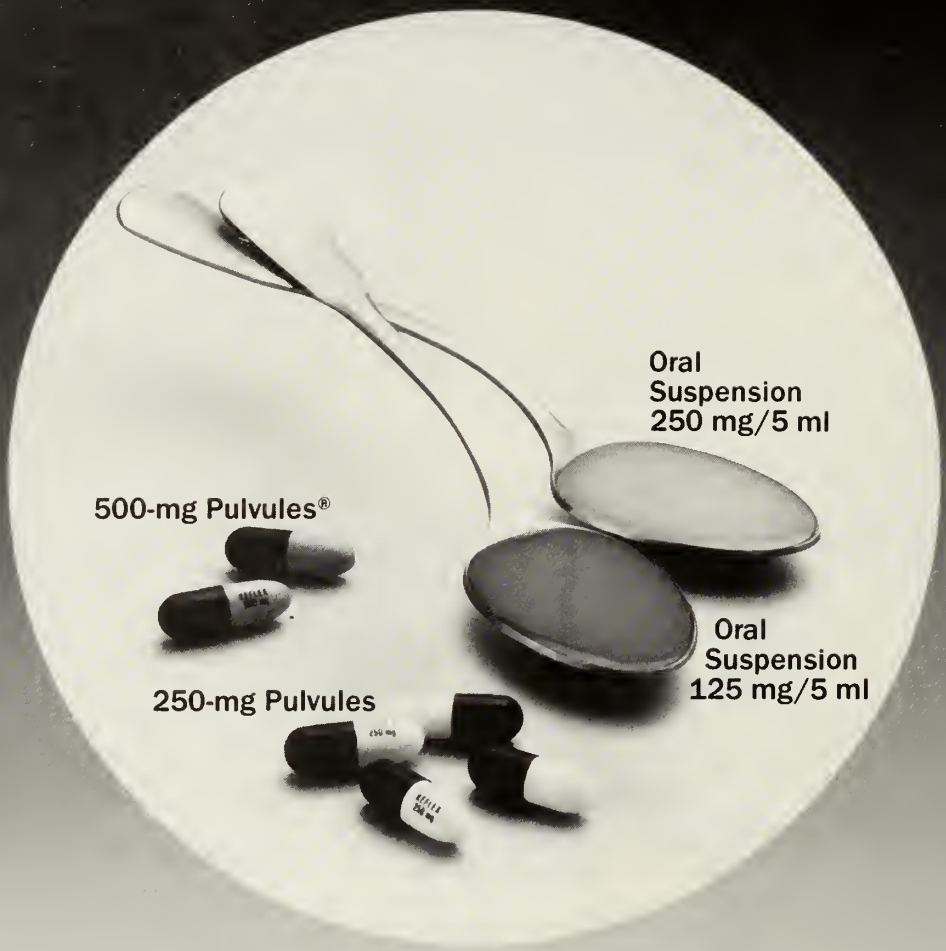
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IN STATE

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November 28
Obstetrical Analgesia/Anesthesia
Place: Sanford
Credit: 2 hours Category I AMA and AAFP
Info: R. S. Cline, MD., Central Carolina Hospital, 1135 Carthage Street, Sanford 27330. 919/774-6518

December 4
Duke Tuesday
Place: Durham
Credit: 5 hours Category I
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

December 5
Tourette's Syndrome
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101. 919/723-3571

December 6-8
Third Comprehensive Symposium on Breast Disease
Place: Winston-Salem
Credit: 20 hours Catetory I AMA
Fee: $350
Info: Postgraduate Medical Sonics, Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 7-March 1, 1985
Postgraduate Course in Medical Sonics
Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: James F. Martin, M.D., Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 9, 1985
A Model for the Development of Gifted Children
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-2482

January 13-16
Beyond Advanced Clinical Teaching Skills
Place: Rougemont
Credit: 20 hours Category I AMA and AAFP
Info: Dr. Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

January 26
Sixth Annual Pulmonary Disease Update
Place: Greenville
Credit: 6 hours Category I AMA
Fee: $60.00
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

OUT OF STATE

November 13
Divorce, Child Custody and the Family
Place: Johnson City, TN
Info: Sue Hutchinson, Quillen-Dishner College of Medicine, Johnson City, TN. 615/928-6426, ext. 204

November 14-17
Williamsburg Symposium on Perinatal Care
Place: Williamsburg
Credit: 12 hours Category I
Fee: $200
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

November 16
Update: Sudden Infant Death Syndrome
Place: Richmond, VA
Fee: $95
Credit: 7 hours Category I AMA, PREP, ACOG, AAFP
Info: Beth Winn, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

December 6-15
Review of Clinical Chemistry Seminar
Place: Snowmass, CO
Credit: 40 hours Category I
Fee: $315
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

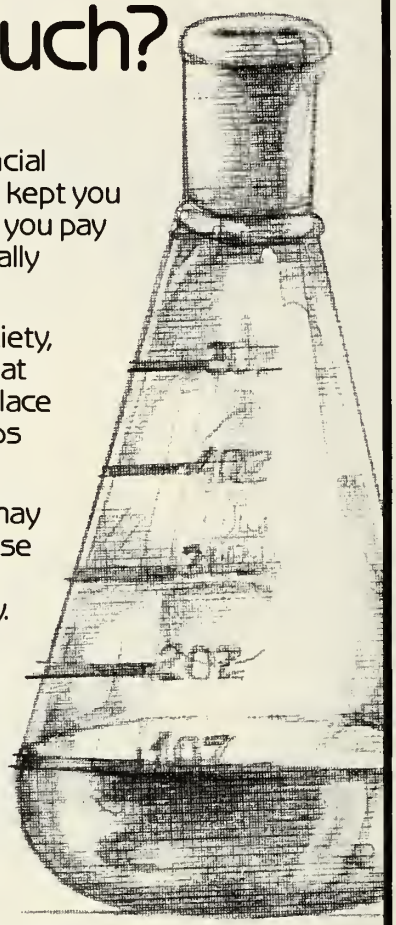
January 17-19, 1985
Advanced Ultrasound Seminar
Place: Orlando, FL
Credit: 14 hours Catetory I AMA
Info: James F. Martin, M.D., Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 22, 1985
38th Annual Stoneburner Lecture Series: Rehabilitation Medicine
Place: Richmond, VA
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

January 26-31, 1985
Dermatology for Non-Dermatologists
Place: Cancun, Mexico
Info: Division of Dermatology, Box 3135, Duke University Medical Center, Durham 27710. 919/684-2504

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What Is Medical Auxiliary: Why Belong?

Linda P. Nance

AS a physician, do you understand what being a member of the North Carolina Medical Society Auxiliary means? The North Carolina Medical Society Auxiliary is a part of the American Medical Association Auxiliary which stands ready to serve its 80,000 members in state and county auxiliaries across the U.S.A.

Through AMA Auxiliary membership, physicians' spouses become a vital part of the health care world. Members are kept up-to-date on new developments in health care delivery through timely and pertinent national publications. The national auxiliary provides materials and project ideas for programs at the state and county levels. State and county auxilians take these projects into schools, hospitals, and homes to meet the challenge of filling community health needs. Promotion of good personal health habits, safety, and fitness form the core of the AMA Auxiliary's goal of quality living for all Americans.

The North Carolina Medical Society Auxiliary, in cooperation with the AMA Auxiliary, has chosen to promote awareness and prevention of child abuse and neglect as its major focus for 1984-1985. Auxiliaries across North Carolina are presenting awareness programs to their members, educators, and community agencies as a result of a child abuse awareness workshop presented at the annual meeting in May.

Because child abuse and neglect affects children and youth of every socioeconomic level, it is important that physicians and their families make themselves aware and become involved in positive community involvement which can identify and attack this growing problem.

North Carolina Auxilians are also being made aware of another problem. There is now a growing awareness of the urgent need for good prenatal and postnatal care if we are to ensure a healthy start in life for babies. Increasingly, health care professionals and volunteer health organizations are promoting prenatal and postnatal care through educational programs and publications. The AMA Auxiliary has developed an informational packet for prenatal and postnatal care, and communities are being encouraged to take an active role in helping to promote personal health habits that will have positive effects on fetal health. Included in the packet is an excellent brochure which is available, free, for distribution in physicians' offices.

As a part of both child neglect and good postnatal care, Auxiliaries are involved in programs to promote the use of child automobile safety restraints. This problem is being addressed in seat loaner programs, school awareness programs, and in promotion of stricter legislation.

In this important election year you can play a part in making sure that medicine's voice is heard. Making your vote count is part of responsible medical citizenship, but you cannot vote if you are not registered! Physicians, physicians' spouses, and eligible family members who are not registered to vote will have no say in electing government officials who will help determine the way medicine is practiced. The American Medical Association Auxiliary is combining efforts with the American Medical Association to conduct a national voter registration drive called PROJECT MEDVOTE to ensure that medicine continues to have a positive effect upon the political process. You can help make PROJECT MEDVOTE a success. If you or your spouse and family are not registered, do it today. Remember that the 350,000 AMA and AMA Auxiliary members plus their spouses, families, and employees equal one million eligible voters.

Child abuse awareness and prevention programs, promotion of good prenatal and postnatal care, and legislation are just a few of the ways in which the Auxiliary can serve as a valuable resource to physicians. Auxilians are involved in promoting a positive image for medicine in your community through many other health education projects.

The PHYSICIAN-SPOUSE TEAM can promote a positive image for physicians in the community, and acts as a strong support system for medical families. Is *your* spouse a member of the Auxiliary Federation: County, State, and National? The North Carolina Medical Society urges every physician to encourage Auxiliary membership for each spouse. Dues can be paid with pre-tax dollars.

For information about membership or for available material, please contact Mona H. Sauls, P.O. Box 27167, Raleigh 27611.

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Letters to the Editor

Training/Educating

To the Editor:

Your editorial in the September issue of the *North Carolina Medical Journal* was great. In your sage, erudite fashion, you covered a difficult area very well.

When I served on the Orthopaedic Residency Review Committee, we differentiated the two in a much less erudite fashion. We said, "You train bird dogs and you educate residents."

I recall your being kidded before about editing "The Duke Medical Journal." I applaud your continuing efforts. We are very proud of them. I did wonder if the article in the same September issue, "Partners in Education in the Academic Medical Center and the Community Hospital," was considered to be "local (North Carolina) advertising."

I echo the sentiments that I hear from my colleagues all over the state when I say we do so very much appreciate what you are doing for us in editing the *Journal*.

Thomas B. Dameron, Jr., M.D.
P.O. Box 10707
Raleigh 27605

To the Editor:

Your editorial "Training Is No Substitute for Education" was truly outstanding. I have shared it with several of my educator friends.

Hervy B. Kornegay, M.D.
238 Smith Chapel Road
Mount Olive 28365

An Omission

To the Editor:

I read with interest the excellent article by Galen S. Wagner, M.D. et al. in the September 1984 edition of the *North Carolina Medical Journal*. I practiced neurology in Cabarrus County for eight years, and can attest to the excellence of the Duke-Cabarrus affiliation and its uniqueness in continuing medical education for the physicians in that part of the state.

I would like to point out an omission. In the early days of the evolution of the Duke-Cabarrus affiliation, Drs. Ladd W. Hamrick, William Anlyan, and Roscoe (Ike) Robinson were most instrumental in the formation of this unique program.

Thanks for an otherwise interesting and informative article.

Marvin P. Rozear, M.D.
Duke University Medical Center
Durham 27710

To the Editor:

I was very pleased to see the letter by Marvin Rozear correcting the oversights in the report of the Duke-Cabarrus Affiliation. Though many were responsible for the inception and the implementation of this program, Ladd Hamrick, Bill Anlyan, and Ike Robinson along with Dr. Stead formed a group which persisted through the years to make certain that this vision became a reality.

Galen S. Wagner, M.D.
Duke University Medical Center
Durham 27710

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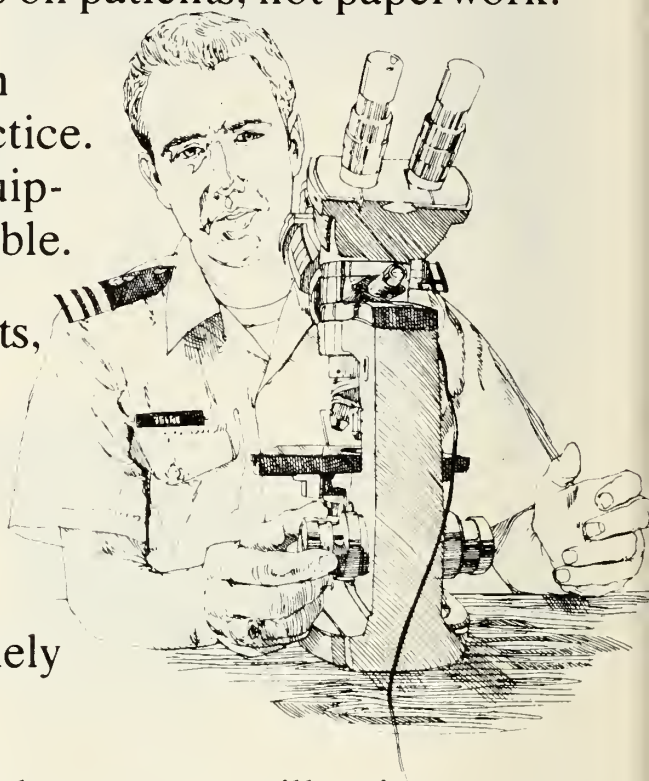
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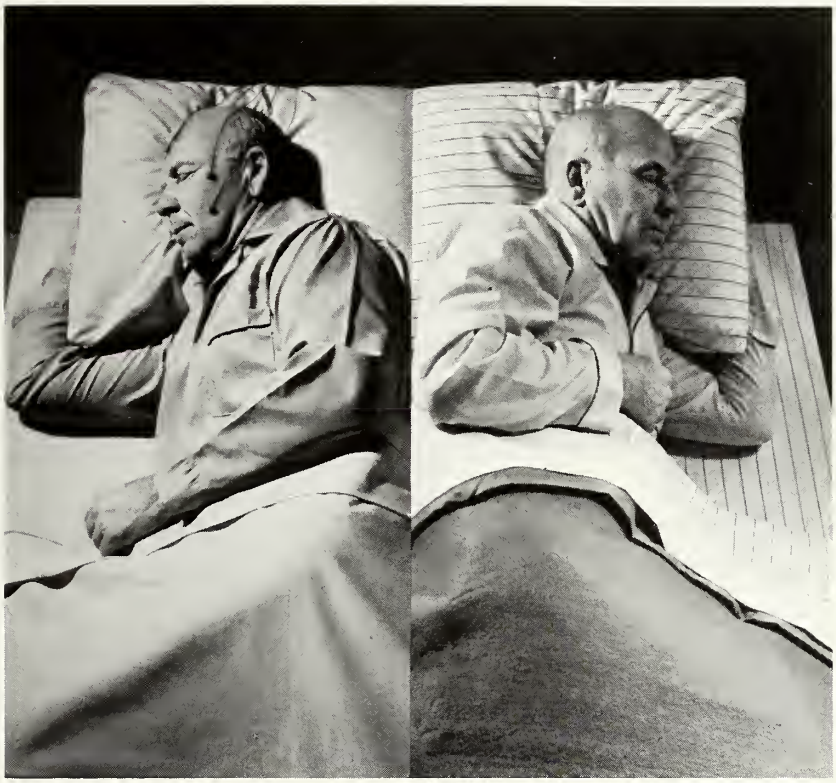
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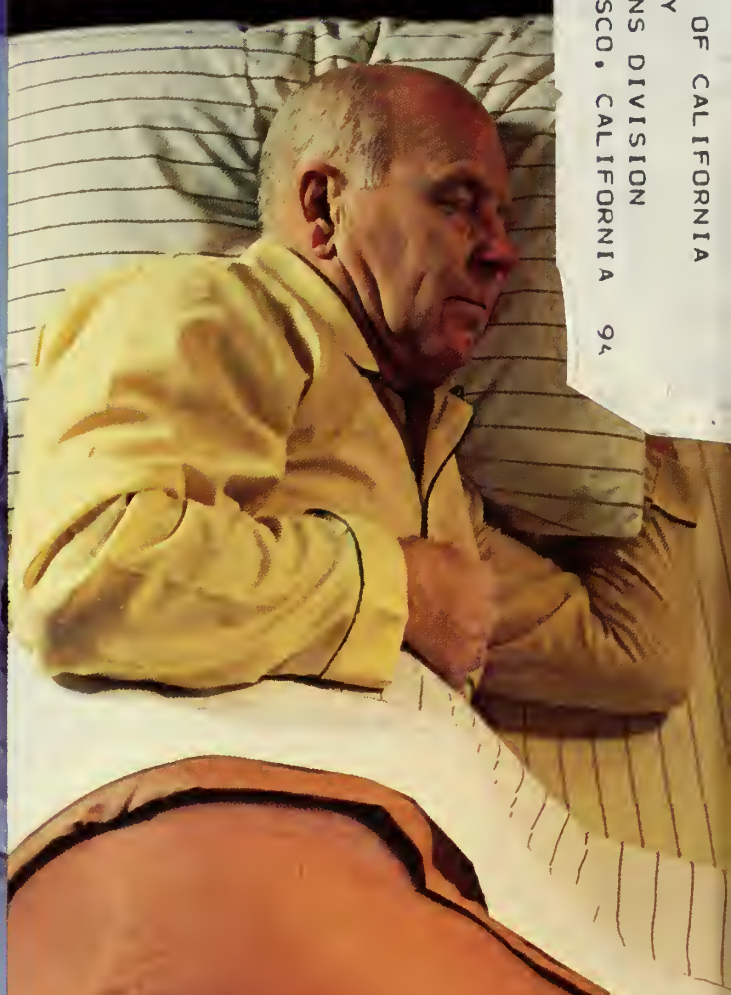
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North Carolina MEDICAL JOURNAL

for doctors and their patients

Official Journal of the NORTH CAROLINA MEDICAL SOCIETY December 1984, Volume 45, No. 12

Holiday Horticultural Happenings, page 791

The ubiquitous mistletoe, a parasite, is also a deadly poison. Other holiday plants and situations can have horrendous complications. Some can even become toxic encounters, by Ronald B. Mack, M.D.



Should We Change Our Admission Policies? — page 762
by John B. Graham, M.D.

Bulimia and Anorexia Nervosa — page 781
by Robert T. Harris, M.D.

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SCIENTIFIC ARTICLE

Treatment of Metrizamide-Induced Mania

J. Ray Israel, M.D. and John Prather, M.D.

• *A patient with chronic arachnitis underwent a cervical CT with metrizamide infusion. This article tells the story of the next eight weeks of treating her side effects.*

MANIA has been reported to be secondary to a number of organic illnesses as well as precipitated by several drugs. Stimulants, including cocaine and amphetamines, phencyclidine, L-dopa, steroids and bromocriptine have been associated with producing mania. Various physical illnesses are also associated with producing mania: toxic confusional states, multiple sclerosis, tumors, particularly in the diencephalon and parasaggital areas, viral encephalitis, hemodialysis, syphilis and epilepsy. The alert clinician must take all of these possibile etiologies into consideration before diagnosing bipolar illness even with a history of depression.

The following case report illustrates the treatment of an organic affective disorder, mania induced by metrizamide. Although there is one other recent report of mania induced by this substance, to our knowledge this is the first reported case that did not resolve with supportive therapy and required extensive treatment. This patient responded to treatment with Lithium Carbonate.

Ms. W, a 38-year-old woman, was admitted to the neurosurgery service with acute complaints of shortness of breath, weakness and trouble standing. Ms. W had a past history of multiple neurosurgical admissions for syringomyelia with repeated cervical, thoracic and lumbar laminectomies and shunting procedures for decompression of her syrinx. A cervical CT with metrizamide infusion was obtained. Findings were consistent with chronic arachnitis with decompression of her syrinx. Within 48 hours of this procedure, Ms. W was confused, disoriented with a euphoric mood. She indicated that she was "jogging and dancing" despite an inability to ambulate without support. A psychiatric consult was obtained and reported the patient seemingly aware with elective mutism and observed smiling and laughing inappropriately. There was no past history nor family history of affective disorder. The differential diagnosis included organic brain syndrome, delirium, atypical dissociative disorder and hypomania. Haldol 2 mg p.o. t.i.d. was initiated as was an organic workup to rule out etiologies of delirium. Her workup (CT scan, EEG, LP, CBC, electrolytes, urine and blood cultures) was essentially normal. Lumbar puncture results — protein 600 mg/dl, glucose 63 mg/dl, cell count WBC 355 with 75% monocytes — were felt consistent with chronic arachnitis. Fungal and bacterial cultures were negative. On follow-up over the next two weeks, Ms. W continued her elated mood with pressured speech and hyperactivity. She was fully oriented and alert. She maintained the delusional percept that she was able to jog and dance. It was decided that her psychiatric symptoms were not secondary to delirium and she was transferred to the psychiatry unit and started on oral fluphenazine hydrochloride 2 mg q.i.d. On the psychiatry unit, her manic symptoms persisted and Lithium Carbonate 300 mg q.i.d. was initiated, maintaining a Lithium level of 0.7 mEq/l. Gradually her manic symptoms dissipated and fluphenazine hydrochloride was discontinued. As her mood became less elevated, Ms. W spoke of depressive themes and her mood became depressed. She was stabilized on trimipramine 150 mg daily with continuation of Lithium Carbonate. Her mental status normalized and she was discharged eight weeks after her cervical CT with metrizamide infusion.

Metrizamide has been associated with several neuropsychiatric side effects including anxiety, depression, drowsiness, confusion and perceptual changes. A higher frequency of these side effects has been found with cervical and thoracic myelography rather than lumbar myelography. With the common usage of metrizamide in radiographic procedures, knowledge of its neuropsychiatric side effects may be increasingly important.

From the Department of Psychiatry, Bowman Gray School of Medicine, Winston-Salem 27103.

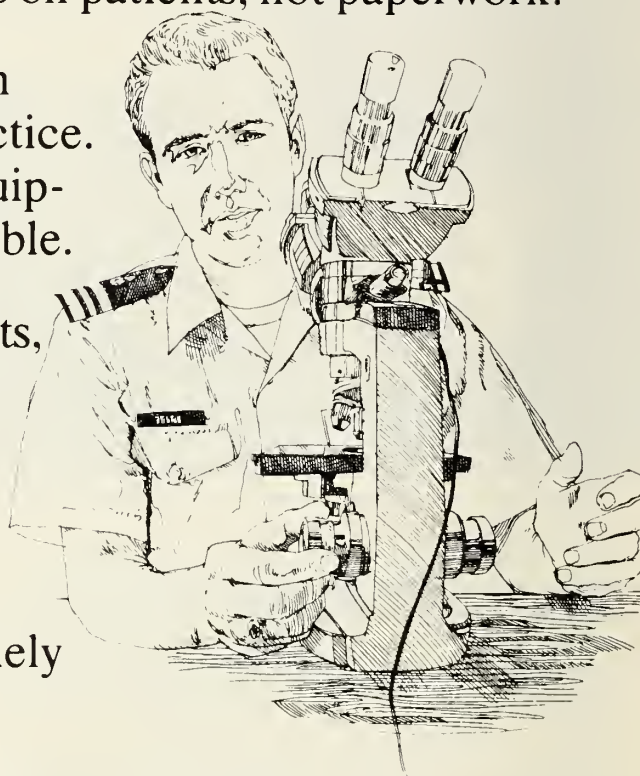
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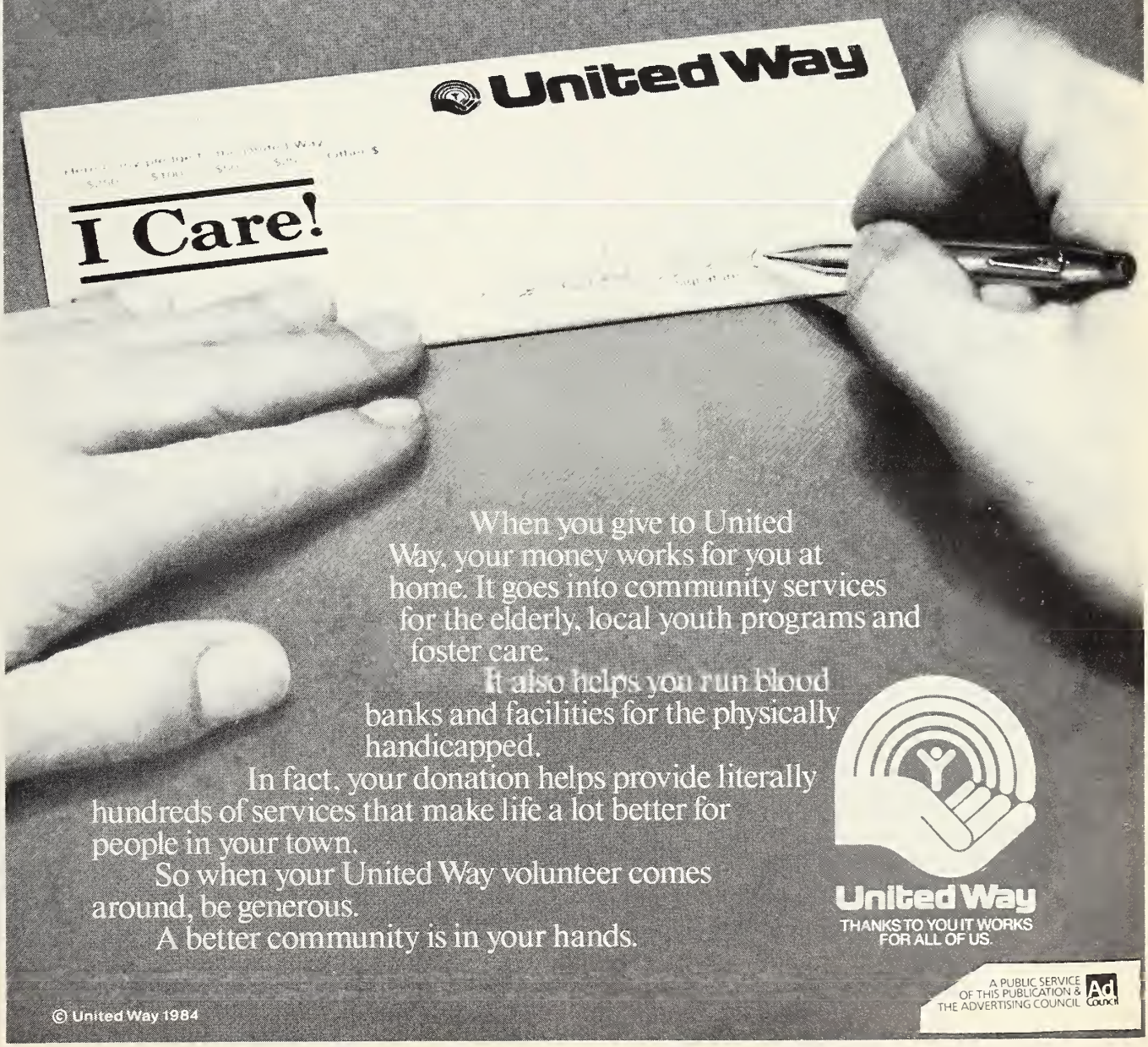
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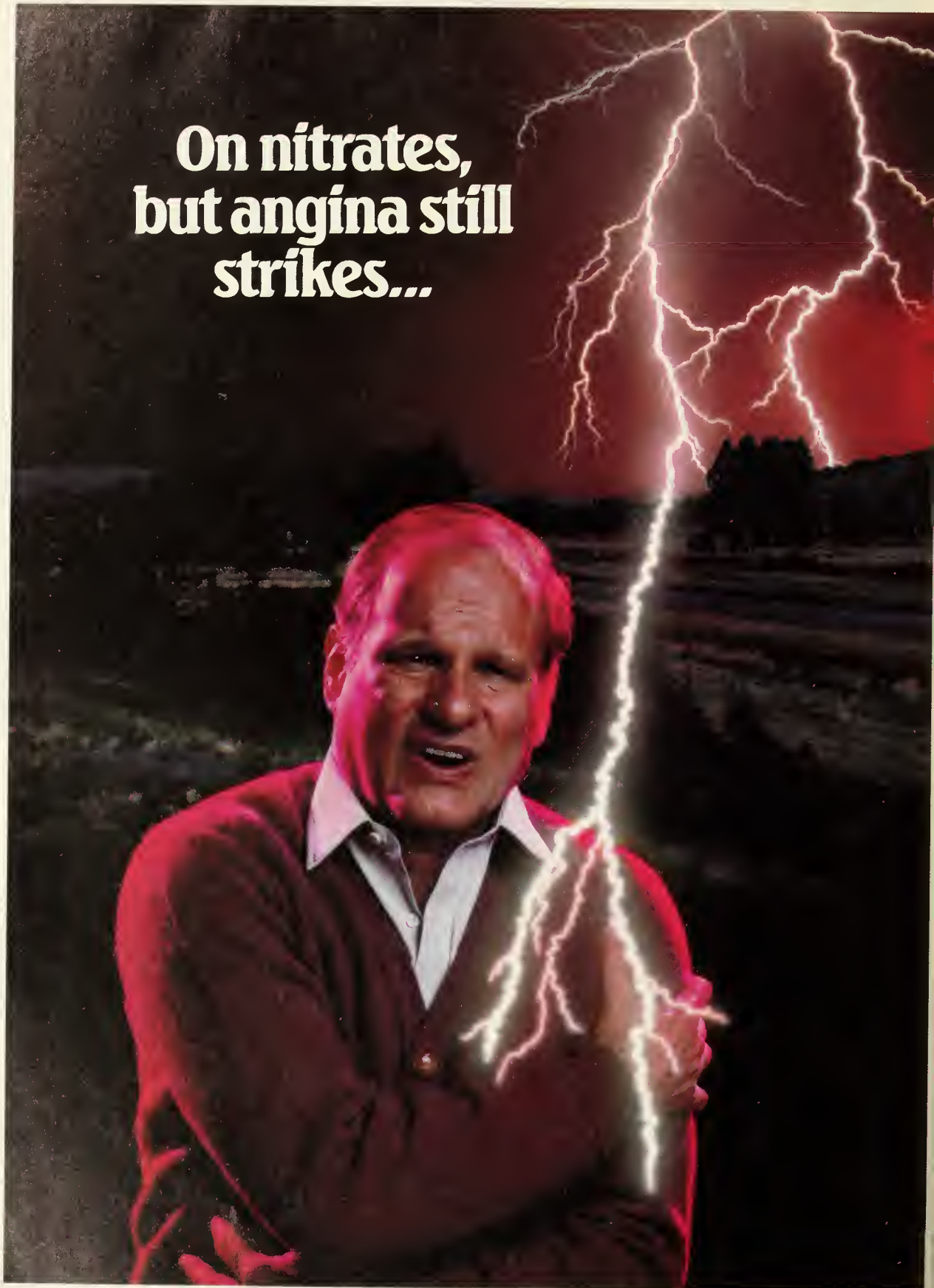
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EDITORIAL

Angioaccess Systems for Prolonged Systemic Therapy of Cancer Patients

William W. Shingleton, M.D.

THE need for easy access to the systemic circulation of patients with malignant disease has increased in importance as a result of the increased use of palliative and curative chemotherapy, the administration of antibiotics, blood and blood products, and intravenous alimentation in these patients. Intermittent venipuncture for these purposes can require considerable effort by the treatment team and discomfort to the patient. Many patients require these forms of therapy over a period of months, or a year or more. The development of new procedures and equipment to address this problem represents a significant advance in the area of cancer patient management. More efficient management of certain other chronic diseases requiring frequent vascular access has also resulted from these technological advances.

Efforts to solve the problem of vascular access were made in the early 1970s by creating an arteriovenous fistula in patients using autologous vein or synthetic material. This approach, although helpful, was found to be limited in its usefulness due to a high incidence of occlusion (30% to 60%). In 1973 Broviac developed a silicone rubber catheter for prolonged venous cannulation and this catheter was modified by Hickman in 1975 by increasing the internal diameter. These silastic catheters were tunneled under the skin distal to the point of entry into a vein (external jugular, axillary, subclavian), with the tip of the catheter located in the superior vena cava. Subsequently, double lumen catheters were introduced which permitted greater flexibility in administering different drugs or other intravenous products simultaneously.

Studies indicate that Hickman-Broviac catheters remain patent for long periods (12-18 months) without occlusion. However, because the catheters require an exit point in the skin, infection has been reported to occur in a range of 10-25 per cent in various patient groups. This problem has led to the development of a totally implanted injection port system that allows for both blood sampling and chemotherapy administration. The system consists of an injection reservoir with a silicone rubber septum connected to a silastic catheter which is positioned into the superior vena cava via the axillary, subclavian, or external jugular vein. A special needle (Huber) is used for insertion into the reservoir located in the subcutaneous tissue of the chest wall, and through this needle blood can be withdrawn, or drugs or other products can be given as indicated. The system is filled with heparinized saline to sustain patency between episodes of active use.

To date, several studies on the use of totally implanted venous access systems for use in cancer patients have been carried out. The largest study involving the evaluation of the device has been performed by investigators at the University of Michigan in Ann Arbor.[1] They indicate that over 100 such devices have now been implanted with more than 29,000 days of access, and with a complication incidence of approximately .6 per 1,000 days of access. Another study reported by Bothe et al,[2] involving 74 patients utilizing a similar implanted venous access system, indicates a somewhat higher incidence of complications. One of the most promising features of these devices is the finding that they can be utilized with a very low infection rate in chronically ill patients who have a depressed immune system. In addition, the device allows successful blood sampling when needed and, at the same time, provides the patient freedom of activity between periods of drug administration. This system, therefore, appears to be a highly reliable, effective, and convenient system with an acceptable complication rate in compromised chronically ill patients. The cost of the system, including installation, is estimated in the range of $500 to $600. Due to cost and other considerations, the system should obviously be used in carefully selected patients whose need for long term angioaccess justifies the cost involved.

A related system has been developed and evaluated for intra-arterial chemotherapy. This system, consisting of a catheter connected to an implantable infusion chamber, is powered by charged freon, has a chamber capacity of 50 milliliters, and a fixed rate of delivery of 3 milliliters a day. The pump is silent, small (10 x 3 cm), and lightweight (180 g). It is refilled and automatically recharged by simple percutaneous injection through the skin every two weeks. The system has been primarily used for perfusion of the liver via the hepatic artery for metastatic liver carcinoma. Balch,[3] who has had a large experience with the device in over 200 patients, has found the system to be highly reliable and largely devoid of the complications associated with conventional intra-arterial therapy, such as sepsis, thrombosis, and misplacement of the catheter. This device is expensive (estimated $10,000-12,000) however, and its value, due to the limited effectiveness of chemotherapy drugs available for use in the system, has yet to be determined.

The angioaccess systems described above for long term intravenous and intra-arterial chemotherapy represent a

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significant advance in the therapeutic management of cancer patients. In the past, one of the major problems associated with long term access systems has been the problem of infection. Evidence now suggests that the newer implantable systems have markedly reduced the incidence of this complication. The additional advantage of these implantable systems is the provision of a portal for long term administration of antibiotics, blood and blood products, and intravenous nutritional products when these are needed.

The use of the presently available implantable device for intra-arterial chemotherapy at this time remains experimental, since the value of this approach for therapy of either primary or metastatic tumor remains questionable.

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EDITORIAL

Should We Change Our Admission Policies?

John B. Graham, M.D.

IT is easy to despair about our future. Nuclear bombs, exploding populations in the Third World, "acid rain," deforestation, hazardous chemicals, unemployment, crime in the streets and by computer, "greenhouse effect," crooked politicians, drug dealing, rapacious property developers, strikes, famines, floods, etc., etc., etc. How can we cope? For one thing, we might try using our intellectual resources more sensibly. These resources consist of the collective minds of our citizens. Two things could be done to utilize them more effectively. We could try to assure that all of the more able minds are trained, and also try to be certain that these trained minds are distributed more effectively for the benefit of our society.

Making certain that the more able are not overlooked early in life is the responsibility of the family and the schools. It is of course important to train the less able, but we are culpable if we fail to train all the more able, those on whom the success of our society depends. It is my impression that we tend to leave the training of our best young people to chance on the theory that they will probably turn out all right. This is very short-sighted.

Let us consider the human trait which we call "IQ." We don't know exactly what it represents, but it is easy to measure and study. We know that high values of IQ tend to be heavily concentrated in a section of the population which everyone agrees also contains our most intelligent citizens. Values of IQ are distributed in what is called a Gaussian (or "normal") fashion. The "mean," or average, value of IQ is given the number 100, and the standard deviation of IQ is 15. This means that 66% of all people have IQs between 85-115. Only 17% have values above 115, and only 5% have values above 125. Our rare geniuses have values above 140.

From the Department of Pathology, UNC School of Medicine, Chapel Hill 27514.

Most of the leaders in any field are drawn largely from those on the upper side of IQ 115. This means that the success of our democratic society depends heavily upon the adequate functioning of less than 17% of our citizens. A society which does not attempt to find and train all of these persons is very foolish indeed.

The evidence is clear that intelligence is unrelated to sex. Whether there is an effect of race on intelligence has been hotly debated for two generations, but I think the question is unimportant. What really matters is that all persons of both sexes and all races have access to adequate training and be encouraged to obtain it.

There is not a surplus of highly able people, and the deficit will become larger as our society becomes more involved with technology.[1] Able women and minority citizens have not always been treated fairly by the schools and employers of our country, and the time is long past when we can afford a loss of talent for reasons of prejudice. I am pleased that in my lifetime we have been moving in the direction of equality, but we have a long way to go.

What is less apparent and, therefore, more troublesome is our failure to perceive the *maldistribution* of our most talented people. Since only 17% have IQs greater than 115, and 5% have values greater than 125, we should be very careful to see that these talents are not overlooked or underutilized. Ignoring short term fluctuations, our country of 250 million people will produce (at our present birth rates) about 3,600,000 babies a year, the yearly output being referred to as a "cohort." Not all members of a cohort who are capable of doing so will finish high school or attend college. But it seems reasonable to estimate that of the 612,000 in each cohort with IQs greater than 115, 500,000

[1] A colleague who has retired has opined that it now requires an IQ of at least 120 to deal adequately with the complexities of medical care, housing, stocks and bonds, income tax, etc.

might complete advanced training. And perhaps 130,000 of the 180,000 with values above 125 will do so. It is these persons on whom we must depend for solutions to the problems which I listed in the beginning.

What are the most important areas of society into which our most talented people should move? Certainly politics, the civil service, the military, and industry are vital areas demanding talent of the highest order. The recent history of our country suggests that these fields have not been receiving the talent that they need. But what about law and medicine, the ancient professions?[2] I believe that law and medicine are much less important than many of my contemporaries, and are not professions which should draw off large numbers of our ablest citizens. But what is actually happening?

Each year the law and medical schools of our country admit more than 40,000 of our ablest graduates. Most of the matriculants come from the upper 5% of the IQ range, a pool of only 130-180,000 in current cohorts (the 1960-62 babies). Thus, it appears that more than one quarter of the best talent becoming available is going into law and medicine. Why? Because we allow the invisible hand of the market place to work its will!

The ancient professions have always been stepping stones socially — acceptable, stable and safe. Now they are also lucrative! It is bad enough to have so many bright doctors on hand that more procedures are done than are necessary in order to protect against malpractice and to maintain incomes. And that there are so many bright and underemployed lawyers that they are causing grid-lock in our courts with unnecessary litigation. But the real danger to our society is not from these actions. It is that these talented people have been removed from general circulation and are not available to tackle more important tasks.

[2] These are referred to as the "ancient professions" because it was the joining together of the faculties of law, medicine, and theology which led to the establishment of the universities in Europe at the end of the Middle Ages.

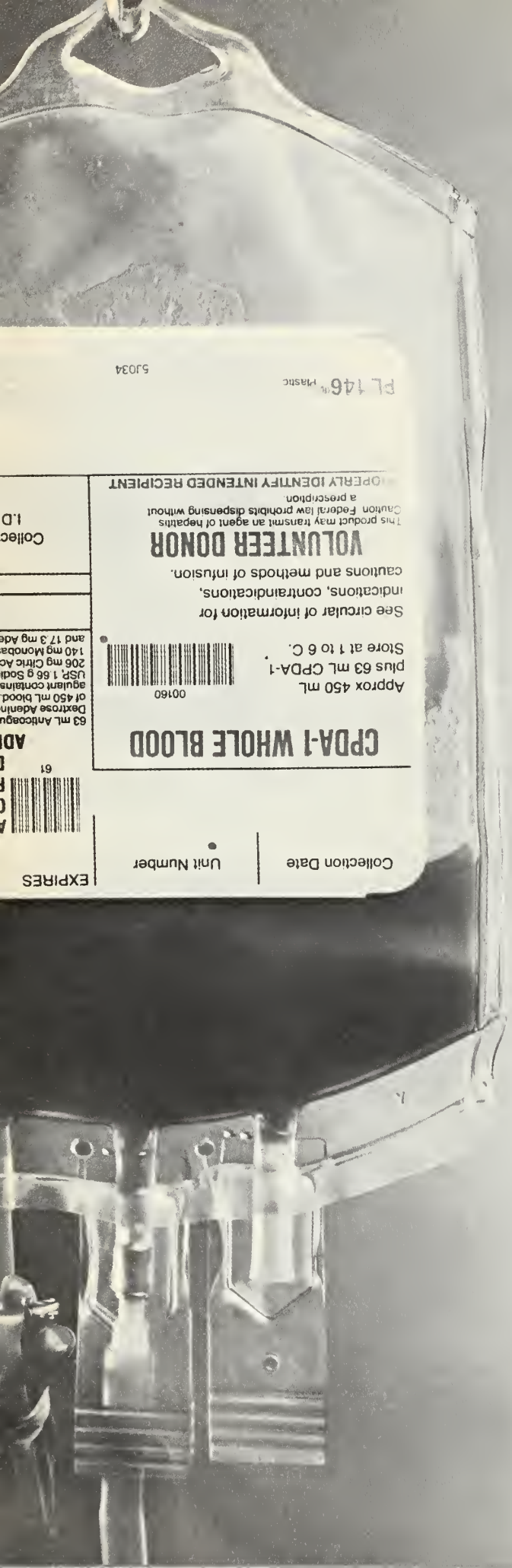
The market mechanism, which became sacrosanct in our country after World War II under the rubric of "free enterprise," is efficient in making short term corrections in our economy. But "bottom line" thinking does not lead to good planning for the long haul. Such thinking has in fact been the cause of many of the problems I mentioned in the first paragraph. In a few years we may find ourselves desperate for talent, because we have allowed too much of it to become sequestered in less essential occupations.

The Dutch are both wiser and more decisive than we. I don't know how they handle admission to law school, but Professor Veltkamp of Leiden tells me that they do not allow medical schools to siphon off too much top talent. Students in the Netherlands are admitted to medical school by lottery.

All students graduating from high school (at least equivalent to our junior college) are eligible for admission to medical school, a six year program. This year about 4000 have applied for 1500 slots. The evaluation process is complex and not entirely random but every applicant stands a chance of admission, including those who have never had a course in science. When such persons are selected, slots are held until deficiencies in science have been remedied.

The Dutch scheme has several consequences. It produces a much wider range of abilities in the medical profession than we have in the USA. This means, among other things, that the profession will contain many more members who are as interested in the personal problems of their patients as in the intellectual problems of their patients' illnesses. The most important effect, however, is that it forces many very able Dutch men and women to move into other sectors of society. This means that the Dutch have a better chance than we to expect future legislatures, military high commands, cabinets, and industries to contain more nearly adequate numbers of the most talented citizens.

Is it any wonder that the Dutch have managed to survive in a hostile environment and to prosper for 600 years? I wish that I felt as hopeful about our own country.



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EDITORIAL

Hypoglycemia: A Handle That Rarely Fits

Warner M. Burch, M.D.

WHAT is hypoglycemia? I find myself addressing that question frequently. Hypoglycemia must be defined operationally as a blood glucose low enough to produce neuroglycopenic and/or adrenergic symptoms. Patients having brain cell failure from hypoglycemia present with an inability to concentrate, confusion, incoherent speech, headache, blurred vision, bizarre behavior, focal or generalized seizures, stupor, coma, and finally death. Adrenergic symptoms relate to homeostatic mechanisms that stimulate release of epinephrine, norepinephrine, cortisol, glucagon, and growth hormone which raise blood glucose in response to hypoglycemia. These homeostatic responses produce the most striking symptoms and include sweating, palpitations, hunger, tremor, tachycardia, and anxiety. These are the early warning signs of hypoglycemia whereas most of the neuroglycopenic symptoms occur when the hypoglycemia is more profound. Two other characteristics of hypoglycemic symptoms are their episodic nature and relief of symptoms with glucose ingestion. Each episode of hypoglycemic symptoms lasts for minutes to hours because either counter-regulatory responses spontaneously raise plasma glucose or the patient eats food to raise the plasma glucose. However, relief of symptoms with food or beverage does not make a diagnosis of hypoglycemia since this is not specific for hypoglycemia.

A diagnosis of hypoglycemia is made when the patient has the symptoms listed above *and* plasma glucose levels are <60 mg/dl after overnight fast (fasting hypoglycemia) or <50 mg/dl on an oral glucose tolerance test (reactive hypoglycemia).[1] Symptoms alone do not make a diagnosis of hypoglycemia. Most symptoms reflect a nonspecific increase in adrenergic discharge. Neither do low plasma glucoses alone establish the diagnosis of hypoglycemia *unless there are accompanying neuroglycopenic or homeostatic symptoms*. Much confusion regarding hypoglycemia can be avoided if these criteria for the diagnosis are met. Fasting hypoglycemia requires full evaluation as to organic causes (e.g., insulinoma).

Many patients make their own diagnosis of hypoglycemia, attributing the symptoms of adrenergic discharge, mental and physical fatigue, and weakness that may or may not be relieved by glucose-laden food to "hypoglycemia." The lay press and media have fanned the fires by popularizing this "entity." Physicians have confused the issue themselves by not having a study that can mimic the conditions under which these patients have symptoms.

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The time-honored oral glucose tolerance test (GTT) has many problems.[2] At least 24% of healthy inductees into the armed forces have 2 hr plasma glucose <60 mg/dl, and 5% have plasma glucose <50 mg/dl without any symptoms. In another study of 650 patients who had no symptoms before or during GTT, 10% had plasma glucose values <47 mg/dl.[3] The frequency of biochemical hypoglycemia is the same for patients who present for evaluation of reactive hypoglycemia as it is for the normal population. Furthermore, most of the patients being evaluated for hypoglycemia with the GTT have symptoms when their corresponding plasma glucoses are in the normal range.[4] The 75-100 g load of glucose is not a physiological challenge since this is not what subjects eat at meals. These factors make interpreting the GTT results difficult. The GTT has a place in making a diagnosis of diabetes mellitus but its use in evaluating hypoglycemia is very questionable. An attempt to use mixed meals (¼-⅓ total daily calories distributed as 50% CHO::20% protein::30% fat) as a challenge that might precipitate symptoms has shown that those patients who have biochemical hypoglycemia on a GTT do not have low plasma glucose after a mixed meal yet have the same adrenergic symptoms.[5] Thus, low plasma glucoses can not be confirmed to be related to symptoms in over 95% of patients in whom the diagnosis of reactive hypoglycemia is tentatively made.

The hordes of patients with "non-hypoglycemic hypoglycemia" or "pseudohypoglycemia" who present to the endocrinologist's practice with the diagnosis of reactive hypoglycemia is astounding. What to say and what to recommend to these people who are looking for a handle to label their symptoms and a means of controlling these symptoms requires clinical discernment. These patients (most often females ages 20-45) have stresses either recognized or not acknowledged. Many have chronic fatigue and somatic complaints lasting days and weeks that do not conform to typical episodic spells of true hypoglycemia. How well these patients are handling stress is reflected in the "hypoglycemic" symptoms. Labeling these patients as having reactive or functional hypoglycemia may be an expedient handle to pacify the patient (and the physician) as to the "physical" cause of the symptoms. However, several weeks or months later, that handle loses its usefulness since the symptoms usually persist or recur. A tender ear and a soft tongue giving an honest assessment of the particular situation is a beginning step in managing these patients. A 120 gm carbohydrate diet low in simple sugars and instructions from an innovative dietician are helpful and should be prescribed. For the recalcitrant patient who has failed to improve despite discussion and diet, psychiatric referral may be helpful.

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EDITORIAL

How the Handle Fit in 1960

Eugene A. Stead, Jr., M.D.

IT has long been recognized that patients with spontaneous or exercise-produced hyperventilation have irritable nervous systems. The fact that the respiratory center does not slow down respiration when enough CO_2 has been lost to produce alkalosis is a sign of incoordination in the regulation of respiration. The patient may be taught to recognize the symptoms of hyperventilation and he may prevent them by breathing into a closed container, as a paper bag, but he will not recover normal smooth control of respiration unless the nervous system functions more normally. He can learn to understand his symptoms and tolerate them and be interested in the situations producing them, but this will not prevent uneven respiratory regulation in times of stress.

The patient with this kind of symptomatology is usually telling the physician two things: (1) his sensory nervous system is unusually sensitive to changes in environment so that changes commonly ignored are now noticed and (2) homeostatic regulation is poor so that swings in the internal environment are greater than normal. Both are responsible for a rather diffuse symptomatology. Examination of the patient shows that he has many evidences of poor homeostatic control. He has cold hands and feet, he sweats profusely in certain areas, goose flesh appears and disappears, and the blood pressure rises too high at times and frequently falls more than expected under the stress of standing. History confirms irregular function of the gastrointestinal tract and the bladder, and difficulty in sexual activities. The laboratory shows both high and low concentrations of blood sugar, the cholesterol varies and the electrocardiogram is unstable.

The physician is likely to attribute the symptoms to the area of his own greatest interest. If he is studying the phenomenon of hyperventilation, this will be the diagnosis. If he is interested in blood sugar regulation, he will believe that he has an instance of functional hypoglycemia. If he is interested in postural reactions, he will attribute considerable importance to the fall in pressure on standing. If he is a gastroenterologist, he will be struck by many similarities between his patient and the "dumping syndrome." If he is a cardiologist, he will be intrigued by the changing electrocardiographic pattern. Because of the dyspnea, and the marked changes in pulse rate, he will summarize his impressions by the diagnosis of "effort syndrome."

In time, the physician is impressed with how little the basic complaint is helped by attention to one aspect of this diffuse disturbance, and he realizes that the patient is describing his overall problem in sensory pickup and regulation of body function, and not a specific disturbance in a single function. He then needs to know what do doctors know about this type of illness and what is its course.

Some persons are born with a sensitive nervous system in which impulses "sprangle" (a fine Carolina term), and in which most sensory impulses cause widespread motor discharges. These patients may always be conscious of their body and the changes in their internal environment. Once they learn about their makeup, they should approach the doctor with the question: "Are these sensations disease or is this I?" Both patient and doctor have to recognize the biologic organization of these particular patients and not be irritated because it differs from others.

The organization of the nervous system and its ability to regulate the internal environment varies greatly in a given person (and, remember, he is different from all other persons) from time to time. The degree to which the system is capable of standing stress without breaking down is a measure of the stability of the system. The system may break down because (1) the stress has become too great or (2) the system is less capable of standing the same stress. By stress, we mean any load, physical, emotional, mental or social which requires additional activity in the mechanisms stabilizing nervous activity and the internal environment of the body. By changes in the system, we mean any disturbance in cell function — be its etiology viral, bacterial, toxic, physical trauma, heat, cold or other physical agents; or caused by alteration in function of the nervous system from emotional or psychic reactions to the environment.

Reprinted from Disease-A-Month 1960;101:25-29.

Many changes in the biology of the patient may occur which are not obvious when the organism is under minimal stress. If we wish to determine the presence of change we must find out if the ability of the organism to stand stress has changed. The stress does not in itself produce the disease, but it does make its presence obvious. A man with moderate coronary disease may have no angina during a relatively sedentary existence. Sudden heavy exertion may produce angina. The exercise has not produced coronary disease. It has merely demonstrated its presence. A patient in his forties may develop urticaria in certain situations in which he never before had difficulty. These situations, which formerly did not end in urticaria, do not produce the biologic changes responsible for the appearance of urticaria, but they do demonstrate that these biologic changes have occurred in the organism. From a practical point of view, the patient needs to know what situations he must avoid in view of the changes in his body.

The fact that patients are able, by their wide testing of themselves in the stresses of living, to find out that their bodies have changed when all of the physician's laboratory findings show no change is not surprising. The patient is reporting the results of a series of biologic assays, and we know from experience that many biologic assays have a sensitivity far beyond that of our present chemical methods. In addition to this difficulty, we do not know all of the active ingredients of any biologic system. Therefore, it is not surprising that the patient describes to us symptoms that we do not understand.

Our knowledge of the symptomatology produced by discrete lesions in the nervous system is still in its infancy. As one watches the changes which occur in an aging population, it is clear that many of their reactions are determined by central nervous system disease. Many of the mechanisms of homeostasis which are reversibly disturbed in the person without destructive disease in the nervous system are permanently crippled in patients with destructive changes in the nervous system. In the early stages of destructive illness, symptomatology may be diffuse and hyperventilation may be present. Only a long followup will determine the kind of illness we are dealing with.

Patients with problems in homeostasis who have symptoms in part from hyperventilation may be grouped as follows:

1. Persons born with sensitive sensory systems and more widespread motor discharges than occur in the average person. These people will always have wide swings in internal environment and in symptomatology. The degree of symptomatology will parallel the physical, emotional, social and economic forces to which they are submitted. The doctor recognizes that these patients are different from the norm, and he teaches them to be tolerant of their bodies. The patient learns what situations provoke undue symptomatology and avoids them.

2. Persons with good homeostatic mechanisms in whom the load becomes too great for the homeostatic mechanisms functioning at a level commonly found in the population. In some way, the load must be lightened.

3. Persons who normally have carried the stress of living without difficulty but who, because of a well-defined illness, can no longer manage the situation. We see this in infections, hepatitis, thyrotoxicosis, pernicious anemia and all other illnesses. Given time, these patients return to their former baseline, provided the precipitating disease can be controlled. Until the usual resiliency returns to the body, additional protection is needed.

4. Persons who can date the time when the body changed to a state of increased sensitivity in the sensory and motor systems. A history of previous episodes in the patient or family is common. At some unpredictable time the patient reverts back to his more normal state. We usually describe these as episodes of self-circumscribed illness characterized by fatigue, depression, loss of sexual drive, unusual sensitivity of the nervous system and poor regulation of the internal environments. Because they feel so bad, many of these patients say that they are carrying heavy loads. The loads certainly seem heavy to the patient, but objective evidence to this effect may not be found. Many of these patients feel quite desperate. They project the future in terms of the present and feel that some organic treatable disease must be found or they will not be able to continue living. The doctor has the great advantage of knowing that the patient will improve in time even if nothing is done. He can help the patient live through the present without anxiety because he knows that the future is not a projection of the present. The doctor uses whatever symptomatic therapy is needed until recovery occurs. He advises the patient against making decisions which will cause large changes in his pattern of living until he feels well again. He uses whatever symptomatic therapy is needed for the patient and himself to live until recovery occurs.

5. Patients with destructive organic disease without localizing signs. This can range from cerebrovascular disease to diffuse carcinomatosis.

6. Patients with a major psychosis may pass through this stage of diffuse irritability of the nervous system.



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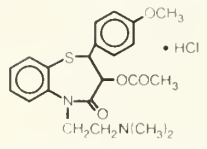
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Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given, a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered.

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
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Public Relations: A Powerful Marketing Tool

Art Stevens

Letter from the Editor to Dr. Charles W. Styron, Chairman of the NCMJ Editorial Board:

Dear Charles:

This is a paper written by a public relations firm hoping to make sales to North Carolina doctors. It is the best statement of the differences between commercial advertising and public relation firms that I have read. What should I do with it?

Dr. Styron's response:

Dear Gene:

The article published herewith presents the differences between overt, unacceptable advertising in medicine versus acceptable means of presenting one's attributes. For years academic centers, clinics, and individuals have "advertised" their wares through professional papers, professional presentations, media announcements of progress in medicine, new techniques, et cetera. Substantial or real progress in medicine has somehow become known to the profession and also to the news media without any effort on the part of the individual or group to make such progress known.

Now there is encouragement by government agencies to make advertising ethical and permissible to all types of professional groups. Fortunately, medicine for the most part has rejected what has been considered unethical advertising.

So today, even in acceptable presentation of medical expertise, there are differences of opinion on how far physicians should go. Some believe in quick and public announcements of what he has to offer. Others believe in time, effort, education, and availability, thus gaining public and professional acceptability the "old-fashioned way, by earning it."

This article presents the differences admirably and for this reason it is made available to our membership.

NOWHERE is change more evident in medicine today than in the tradition-shattering idea of promoting private medical practice through the standard marketing techniques of advertising and public relations.

Promotional methods now available to every medical care professional have, like medical technology itself, moved far beyond the horse-and-buggy era. Yet, almost a decade after the Supreme Court and Federal Trade Commission rulings setting aside restrictions against advertising by professionals, controversy continues unabated about such uses.

Historically, restraints on advertising were instituted to protect a medically unsophisticated public from falling prey to the unscrupulous. Even today, years after promotion became an issue, so strong is the suspicion of an alliance between advertising and purely selfish motives that its employment can still stigmatize the user.

From Lobsenz-Stevens, Inc., 460 Park Avenue South, New York 10016.

These circumstances present the medical profession with a new challenge: to develop methods of expanding its channels of communication with an information-hungry public without transgressing reasonable ethical guidelines. The situation calls for methods which provide the public with responsible information and at the same time preserve respect for the dignity and standards of conduct of the medical profession. One such acceptable method is public relations.

Differences Between Advertising and Public Relations

While both advertising and public relations are powerful aids in helping shape public perceptions and attitudes, there are some basic differences in reader response to them.

Both advertising and public relations deal in information. While the purpose of information in advertising is to induce a desire to buy, in public relations information is used primarily to promote good will and understanding.

Space in which advertising appears is purchased; public

relations space is not. Advertisers exert total control over the information they present in the purchased space and the amount of information presented is limited by cost alone. On the other hand, control of public relations information rests with the media and is presented only when it meets rigid media criteria of newsworthiness or beneficial public information. Consequently, because pr information is filtered through newscasters, reporters and editors, these third-party reports seem more objective and therefore often more believable.

Growing Public Hunger for Medical Information

Despite the fact that self-promotion efforts raise some eyebrows within medical circles and prompt discussion of appropriate ethical guidelines, the trend toward such promotion has been growing steadily for several years. This has happened because the public is eager for more medical information.

In response to this emerging public appetite, all the media have expanded their coverage of medical facts and developments. This circumstance has made it possible for farsighted medical people to utilize the situation effectively. By making it part of their professional duty and responsibility to engage in providing the public with reliable, comprehensible, up-to-date information, they enlighten the public and simultaneously promote themselves.

Public Relations Methods Vary Widely

Public relations offers a variety of opportunities to engage in this process: guest appearances on discussion shows on radio and television; "how-to" books on medical subjects; guest editorials on specific health or fitness-related topics; articles written by or quoting a medical professional; syndicated health and fitness columns; participation as speakers in local groups and meetings where issues related to medicine may be part of the agenda. Each of these activities provides a needed public service. In addition, each represents a powerful way of increasing public awareness of a specific physician and that individual's expertise. Such opportunities are having a profound influence on how professionals can build and enlarge their practices. Compared with these uses of the media, the old hanging-out-a-shingle-and-listing-oneself-in-the-yellow-pages lacks impact. And waiting for word-of-mouth referrals takes many years.

What to Expect From Public Relations

Responsible pr professionals have guidelines which enable them to help medical specialists market themselves honestly. If you use public relations help, you can rightly expect the following:

1. Your name before a wide public. Public relations can achieve enhanced recognition quickly and associate your name with a specific set of skills.
2. Public awareness of your viewpoint, outlook, expertise.
3. A balanced campaign employing national, regional and local exposure, as appropriate to your objectives.
4. A systematic campaign with a timetable, written plan, set of themes for articles, scheduled interviews and regular progress reports. These make it possible to monitor results.
5. Ongoing interaction with your agency.
6. Identified objectives well suited to your marketing needs. These needs will vary as specialties themselves vary. For example, if the specialty is otolaryngology, the pr campaign might include:

- An article in a national consumer publication, such as *The Saturday Evening Post,* on "Hearing Impairment: Who Is At Risk?"
- An article in a national consumer publication, such as *Time* or *Business Week,* on "How to Counter Negative Public Attitudes Toward Hearing Loss."
- Appearances on TV programs — national or local — to discuss latest diagnostic and surgical procedures in hearing loss treatment.
- Releases to health/medical editors of national women's, men's and general interest magazines, large circulation daily newspapers and news syndicates on treating hearing loss.
- Speaking engagements to reach specific regional groups dealing with hearing loss: the elderly, high risk groups in industry, etc.

These examples illustrate how a pr campaign can reach a national audience, a specific local group or both. It can gain attention, educate, alert, inform — and achieve these tasks effectively and responsibly.

Health care providers employing public relations can expect to become much better known and to be sought after by people who are in need of the precise medical services they provide. Moreover, these activities can bring honor, recognition and credit both to themselves and to their colleagues. At the same time the entire marketing effort can be accomplished in an ethical, dignified, professional manner.

What I Needed to Know About Cyclosporine

James T. C. Li, M.D., Ph.D.

• *How effective an immunosuppressant is cyclosporine? This article reviews its pharmacology and mechanisms, effectiveness and side effects in clinical studies performed over the last several years.*

I recently had occasion to take care of a patient who had been on cyclosporine immunosuppression following a bone marrow transplant. Not knowing much about cyclosporine, I went to the library to find a review article to read. Was cyclosporine the ideal immunosuppressant? Was it effective in all types of transplantations? What were the side effects?

There were abundant reports on pharmacokinetics, putative mechanisms of action, and several reports of clinical trials but no single paper reviewing all relevant aspects. This brief report contains the salient points distilled from more than 50 articles on cyclosporine. The information should be useful to any physician who has a patient taking cyclosporine.

Cyclosporine is a new immunosuppressive agent recently approved for general clinical use by the FDA. The introduction of this new drug has been enthusiastically received by physicians involved in clinical transplantation. Cyclosporine has proved to be equal or superior to conventional immunosuppressive therapy in terms of both patient survival and graft survival in all studies. Liver and heart allograft recipients in particular have greatly benefited from cyclosporine immunosuppression. All this without myelosuppression and with reduced doses of corticosteroids!

Unfortunately, cyclosporine is also nephrotoxic. Pilot studies in renal transplant recipients revealed frequent post-transplant oliguria, acute tubular necrosis, and graft failure, but this high degree of nephrotoxicity now can largely be avoided by carefully adjusting doses. A recently developed radioimmunoassay capable of easily measuring cyclosporine dosing levels may decrease clinical nephrotoxicity further still.

The preliminary reports of several randomized, prospective trials in renal and bone marrow transplantation have recently been published. The collective data suggest that cyclosporine is equal, but not clearly superior, to conventional immunosuppressive therapy in these two applications.

Pharmacology

The cyclosporines are cyclic peptides extracted from soil fungi. Cyclosporine A is extracted from the soil fungus *Tolypocladium inflatum*. Biological screening showed this compound to have potent immunosuppressive properties without myelotoxicity, and subsequent animal studies demonstrated the effectiveness of cyclosporine A in transplantation. Presently, as the only one of the cyclosporines approved for clinical use, it is called simply cyclosporine.

Cyclosporine consists of 11 aliphatic aminoacids. This accounts for the hydrophobic nature and poor water solubility of the drug. Because of these properties, cyclosporine is administered orally in an olive-oil based solution; it can also be administered intramuscularly or intravenously. Following an oral dose, peak blood levels are detected in 2-3 hours. Bioavailability varies between 20 and 50 percent.

Cyclosporine is metabolized primarily through the liver with less than 6 percent excretion in the urine. Various metabolites of cyclosporine have been identified in humans but their immunosuppressive properties are not known. The study of a renal transplant recipient who required an ileostomy demonstrated biliary excretion and probable enterohepatic recirculation of cyclosporine and its metabolites.

The terminal half-life of cyclosporine has been estimated at 14-17 hours. Factors complicating precise pharmacokinetic measurement of serum half-life include the distribution of the drug into body tissues and the aforementioned enterohepatic circulation. Cyclosporine is usually administered orally as a single daily dose.

Clinical Studies

A number of large, well-designed, randomized prospective studies are going on that compare cyclosporine with conventional therapy. The experience in renal transplantation is by far the most extensive.

The results of a European Multicenter Trial comparing cyclosporine with azathioprine and steroids in renal allograft recipients show estimated six-month graft survival probabilities of 73 percent and 53 percent, respectively.[1] Similarly, the Canadian Multicenter Transplant Study Group compared cyclosporine and prednisone with conventional therapy in cadaveric renal transplantation. Both graft survival (80.4% vs 64%) and patient survival (91.1% vs 89%) improved in the cyclosporine group.[2]

On the other hand, prospective trials at the University of Minnesota and University of Sydney, Australia, showed excellent but equivalent success in the cyclosporine and control groups when patient and graft survival was com-

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pared. The cyclosporine groups in these trials manifested some benefit in terms of fewer readmissions, fewer acute rejection episodes, lower hospital costs, fewer steroid side effects, and decreased myelotoxicity. It is not yet known whether the combination of cyclosporine and steroids is superior to cyclosporine alone.

A number of conclusions can be drawn from this widespread experience. Renal function in the cyclosporine groups averages 10-20 percent lower than in control groups, but this degree of renal insufficiency remains stable over time. Merion and colleagues have followed cyclosporine renal transplant recipients for up to 4½ years and have not observed progressive deterioration of renal function. It is not known whether careful monitoring of serum cyclosporine levels by radioimmunoassay can reduce cyclosporine nephrotoxicity.

The high incidence of lymphomas in pilot studies has not been confirmed by later studies. Lymphoproliferative disorders probably occur in 1-2 percent of cyclosporine-treated patients, similar to conventional immunosuppression. Bacterial infections in renal transplant recipients also appear to be equivalent in cyclosporine and control groups, while fewer CMV infections may occur in cyclosporine-treated patients. Heart transplant recipients treated with cyclosporine clearly exhibited a lower mortality from infectious causes (8% vs 40%). Other major effects of cyclosporine include hepatotoxicity, gingival hypertrophy, hirsutism, and tremor.

Initial reports suggested that cyclosporine was superior to conventional therapy in bone marrow recipients as well. The enthusiasm dampened, however, when the preliminary results of two ongoing randomized prospective trials showed no significant difference between the two groups in terms of both patient survival and graft-versus-host disease. As with all preliminary reports, no firm conclusions should be drawn until these and other controlled studies are completed.

Cyclosporine has greatly improved success in liver transplantation. The success has been so impressive that it is highly unlikely that a randomized trial will ever be performed. The University of Pittsburgh reports that 42 of 67 consecutive liver transplant recipients survived 1 year or more (63%).[3] This compares favorably with a 33 percent one-year survival in the pre-cyclosporine era.

Similarly, cyclosporine has significantly lowered mortality in heart transplant recipients. At Stanford, overall mortality has dropped from 62 percent to 21 percent since the introduction of cyclosporine immunosuppression. However, two adverse effects of cyclosporine have been observed in heart transplant recipients: 1) hypertension develops in most patients; 2) myocardial fibrosis has been detected by biopsy or postmortem examination. Present information suggests that this fibrosis is not progressive and does not lead to hemodynamic compromise, but further study is needed to fully assess its long-term significance. The role of cyclosporine in transplantation is summarized in table 1.

Last but not least is the experience in heart-lung transplantation. This dramatic operation is performed in patients with end-stage pulmonary hypertension. Before cyclosporine immunosuppression was introduced, survival was measured in days. Jamieson and co-workers have recently reported their experience with 13 heart-lung transplant recipients, all of whom received cyclosporine as part of their immunosuppressive regimen.[4] Ten patients were alive at the time of publication, four patients having survived more than 12 months and one patient alive after two years. Cyclosporine has certainly made a significant impact in this field!

Mechanism

Although the mechanism of action of cyclosporine has not been fully elucidated, recent data demonstrate that cyclosporine interferes with T-cell activation (reviewed in 5). These studies show that cyclosporine inhibits the production of Interleukin II. This factor is produced by helper T-cells and is essential for cytotoxic T-cell activation and proliferation. Other proposed mechanisms of cyclosporine immunosuppression include the suppression of interferon production, the facilitation of tolerance induction, and the generation of suppressor cells. The effects of cyclosporine at the molecular level are unknown.

Conclusions

Cyclosporine is an effective immunosuppressant which is superior to previous therapy in heart and liver transplantation and at least equal in effectiveness in renal and bone marrow transplantation. Nephrotoxicity remains an important problem and may limit its overall applicability. The incidence of drug-induced lymphomas appears similar to that of conventional immunosuppressive therapy. As the mechanism of T-cell activation unravels, other inhibitors of T-cell function may well be developed. One can expect these new immunosuppressive agents to be utilized in applications beyond clinical transplantation.

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Table 1.
Cyclosporine Compared with Conventional Immunosuppression

Donor Organ	Efficacy
Kidney	Equal or Superior
Bone Marrow	Equal
Liver	Superior
Heart	Superior
Heart-Lung	Superior

Clinical Uses of Anti-Thymocyte Globulin (ATGAM), Part II

Colleen Gilbert

Aplastic Anemia

ATGAM is currently undergoing active investigation for therapeutic efficacy in the treatment of aplastic anemia.[15, 20, 21, 36, 37] Aplastic anemia is an often fatal disease of bone marrow suppression in which there is inadequate production of erythrocytes, as well as granulocytes and platelets in severe cases.[36, 38] An immunological component has been postulated to be involved in the pathogenic mechanism of this disease. The humoral or cellular immunity may be involved by inhibition of stem cell development or lack of hematopoietic cofactors. Bone marrow transplant is the therapy of choice if a suitable donor can be found. Unfortunately, this is often not possible and various medical treatments have been used, including androgens, steroids, cyclophosphamide, and ATG. ATG may work by decreasing the number of T suppressor cells that may be acting on the hematopoietic stem cells, or it may alter the release of soluble factors which may be involved in the pathogenesis of aplastic anemia.[36] Several studies have been published which evaluate ATGAM therapy in aplastic anemia. There is at least one multicenter trial in progress in which Duke is participating.

Preliminary trials of ATGAM for severe aplastic anemia involved a small number of patients and used ATG only in conjunction with other agents such as steroids and androgens. Approximately 50% of patients responded to ATG given 10-15 mg/kg over 10-14 days.[15, 18, 37] Champlin et al evaluated ATGAM for moderate to severe aplastic anemia in a prospective, randomized trial.[21] They demonstrated a substantial benefit from ATG given 20 mg/kg/day for eight days. Patients were premedicated with acetaminophen and diphenhydramine 30 minutes prior to infusion and 25-50 mg hydrocortisone was used to control chills and urticaria. A total of 42 patients was enrolled in the study and the 21 controls received supportive care only. After three months, 12 of the control patients also received ATG so that a total of 33 patients was treated, of which 19 responded to ATGAM therapy. Response to ATGAM was defined as elimination of transfusion requirements or only occasional platelets required. All patients exhibited some symptoms of serum sickness in 6-18 days of ATG therapy, which was controlled by prednisone 40 mg/m^2 tapered over two weeks. Champlin recommended initiation of ATGAM therapy within four months of disease diagnosis, since there appears to be an inverse relationship between positive ATG response and duration of aplasia.

Bone Marrow Transplantation and Graft-vs-Host Disease

Anti-thymocyte globulin has been considered for immunosuppressive adjunctive therapy for bone marrow transplantation, prophylaxis for graft rejection or the development of graft-versus-host disease (GVHD). GVHD is a major complication of bone marrow transplantation. It occurs in 30-50% of marrow graft recipients despite HLA matching and immunosuppression.[24] Basically, it is a reaction of donor lymphocytes against the recipient which can take many forms. Manifestations of GVH disease may include debilitating skin disease, severe oral and esophageal mucositis, malabsorption, pulmonary insufficiency, liver disease and recurrent bacterial infections.[26]

Speck et al have used a Swiss equine ATG in conjunction with bone marrow transplantation.[19] They compared results of three groups: Group A (n = 18) — HLA matched sibling bone marrow graft plus cyclophosphamide 50 mg/kg x four days — 44% survival; Group B (n = 20) — LRD graft plus ATG 40 mg/kg x four days plus norethandrolone — 74% survival; and Group C (n = 12) — ATG 40 mg/kg x four days plus norethandrolone, no donor — 67% survival. There was no GVH disease in group B, while group A experienced six deaths due to GVHD and two survivors have chronic GVHD.

Ramsey et al conducted a randomized trial to compare two regimens in the prevention of acute graft-versus-host disease.[25] Patients were all recipients of HLA matched sibling bone marrow and were being treated for aplastic anemia or leukemia. Prophylaxis of GVHD has included methotrexate post-transplantation therapy, *in vitro* treatment of donor marrow with anti-T cell globulin, and immunosuppression with cyclosporine or ATG after transplantation. In this study, 35 patients were given methotrexate (MTX) 15 mg/m^2 IV one day post-transplantation, then 10 mg/m^2 on days 3, 6, and 11, followed by weekly injections up to 100 days. Another 32 patients received the same methotrexate regimen plus 15 mg/kg ATG QOD for seven doses beginning on day 8 and oral prednisone 40 mg/m^2 on days 8-20. A total of 48% of the MTX group developed some manifestations of GVHD, while only 21% of the MTX, ATG and prednisone group developed GVHD. The ATG used in this study was prepared at the University of Minnesota.

Another preliminary trial of prophylaxis and treatment of

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GVHD with ATGAM was conducted in Seattle by Weiden et al.[39] Eligible patients received HLA matched sibling bone marrow for treatment of hematologic malignancies and had not received any ATG previously. All patients received MTX post-transplantation according to the regimen described previously. When definite evidence of early engraftment was seen, 17 patients were randomized to receive prophylactic ATG and 12 patients were randomized as controls. Ultimately, 12 patients were given ATG, 7 mg/kg QOD for six doses beginning one to four weeks post-transplantation. The patient population was small but did indicate some benefit from using ATG. GVHD developed in three of 12 ATG patients and in six of 12 control patients. This group also used the same low dose ATG to treat nine patients for GVHD. Control patients (n = 6) were treated with prednisolone for 10 days. Results were not conclusive, due to the small patient population. However, both ATG and steroids resulted in improvement of GVHD in most patients. This same group of investigators went on to conduct a randonized trial comparing ATG and corticosteroids in the treatment of GVHD in allogeneic marrow graft recipients.[24] The conditions and ATG dosage were the same as previously described. Patients who could not tolerate IV equine serum were given rabbit ATG intramuscularly. The study looked at 20 patients receiving steroids and 17 patients receiving ATG. No significant differences were noted between the two regimens in the primary treatment of acute GVHD.

Other Uses

Anti-thymocyte globulin has been considered as adjunctive therapy in a variety of other disease states. Due to ATG's effect of temporarily but significantly reducing circulating T cells, it has been used in non-Hodgkins lymphomas, Sezary syndrome and T-cell leukemias.[22, 23] Studies to date are small and inconclusive. Thus far, long-term beneficial effects have not been documented. Immunosuppression, including ATG, has not been demonstrated to be superior to placebo in the therapy of multiple sclerosis.[27] There have been some promising results in the treatment of another autoimmune disease, myasthenia gravis. Pirofsky noted some response in eight of 10 patients treated with low dose daily ATG.[28, 29] Larger, well controlled studies will be needed to substantiate this preliminary work. Finally, ATG has been used in a small number of severely burned patients in conjunction with skin allografting.[3, 14] ATGAM was preferred to azathioprine by this Harvard group, due to the more prolonged, non-specific marrow suppression seen with azathioprine. This group uniquely controlled ATGAM dosage by monitoring degree of T-rosette inhibition.

Clinical Toxicity, Prevention and Management

The fundamental nature of ATGAM is that of a foreign horse protein. As such, ATG has a high potential to stimulate immunogenic responses in the human host. Early side effects which were expected and have been documented include chills, fever, erythema, pruritis, serum sickness and anaphylaxis. Chills and fever are most common and occur in one third of all patients.[2] The incidence of anaphylaxis is low (<1%), although ATG skin testing is always performed before administration.[2] Widely disparate reports of serum sickness occurrence are apparently related to the degree of concurrent immunosuppression and the use of corticosteroids. The incidence of this problem in renal allograft recipients is less than 1%; however, in therapy of aplastic anemia some symptoms of serum sickness occur in virtually all patients at about day 8-16.[20]

Other important early side effects include leukopenia (14%), thrombocytopenia (11%), erythema and pruritis (12.5%), local phlebitis (12.5%) and hemolysis (<1%).[2] Thrombocytopenia is thought to be due to the presence of anti-platelet antibodies in the ATG, because of the common surface antigens of platelets and thymocytes.[40] This causes platelet aggregation and, in the presence of complement, lysis (although complement is not necessary for the anti-platelet effect).[40]

Serious, delayed toxicity has been feared with the use of this agent. Actually, there has been no significant increase in neoplasias, mortality, anti-glomerular basement membrane injury, or aseptic necrosis.[2] Some increase in sepsis by viral or fungal agents has been reported but this is no different from that seen with high dose steroids and azathioprine.[35]

Before administering ATG a skin test must be performed. An intradermal injection of 0.1 ml of a 1:1000 dilution in normal saline is given with a saline control.[2] Caution should be used if a wheal, erythema, itching or local swelling occur. ATGAM is contraindicated if a generalized rash, tachycardia, dyspnea, hypotension or anaphylaxis occur. It is important to realize that an allergic reaction may still occur from ATG therapy despite a negative skin test. Privately produced goat and rabbit anti-thymocyte globulin is available in this country for patients who cannot tolerate equine serum. Patients should, of course, be skin tested before these preparations are utilized.

The recommended dosing regimen for ATGAM is 10-15 mg/kg/day for 14 days, then QOD for 14 days.[2] Begin administration within 24 hours of renal transplant or when allograft rejection is diagnosed. Dosage for investigational uses is not clearly defined, although this regimen is similar to protocols using ATGAM for aplastic anemia. ATGAM must be diluted to 1 mg/ml in 0.45% or 0.9% saline solutions. The total time during which the product is diluted should not exceed 12 hours, including administration time. Infuse slowly, over 4-8 hours, through a central line (preferably with an in-line filter). This will help minimize phlebitis and thrombosis. Do not mix ATGAM with 5% dextrose, as low salt concentrations cause precipitation of drug.[2] Also, avoid highly acidic solutions which are incompatible with ATGAM.[2]

In order to minimize many of the early side effects of ATG, patients may be premedicated with acetaminophen and diphenhydramine. Hydrocortisone (50 mg) or methylprednisolone (40 mg/m^2) may be administered during ATG infusions. In addition, prednisone 5-20 mg QID is recommended throughout ATG therapy.[2] Immediately halt ATGAM therapy if any anaphylactic-type reaction occurs and administer 0.3 ml aqueous epinephrine (1:1000) intramuscularly. Provide appropriate resuscitative measures and do not resume ATG.[2] ATGAM is available in 5 ml vials containing 250 mg equine globulin stabilized in 0.3 M

glycine and preserved with 0.01% thimerosal. The acquisition cost is $87.50/5 ml vial.

Summary

Anti-thymocyte globulin has undergone extensive evaluation as an immunosuppressive agent in clinical transplantation and autoimmune disease. Its benefit has been established in prophylaxis and treatment of renal allograft rejection. Results are promising in investigational study of ATGAM for aplastic anemia. *In vitro* and *in vivo* assays, currently used to define ATGAM activity, have not clearly correlated with clinical efficacy. Development of more predictive assays and monitoring criteria will certainly improve the utilization of ATG. In the future, improved production of specific anti-T cell serum will continue with the use of hybridoma techniques to develop monoclonal antibodies.[41] Anti-thymocyte globulin is a valuable immunosuppressive agent used alone or in conjunction with other agents such as azathioprine and corticosteroids. Future studies will further define the role of this agent in various disease states and should provide some interesting clinical comparisons with other new drugs such as cyclosporine.[30]

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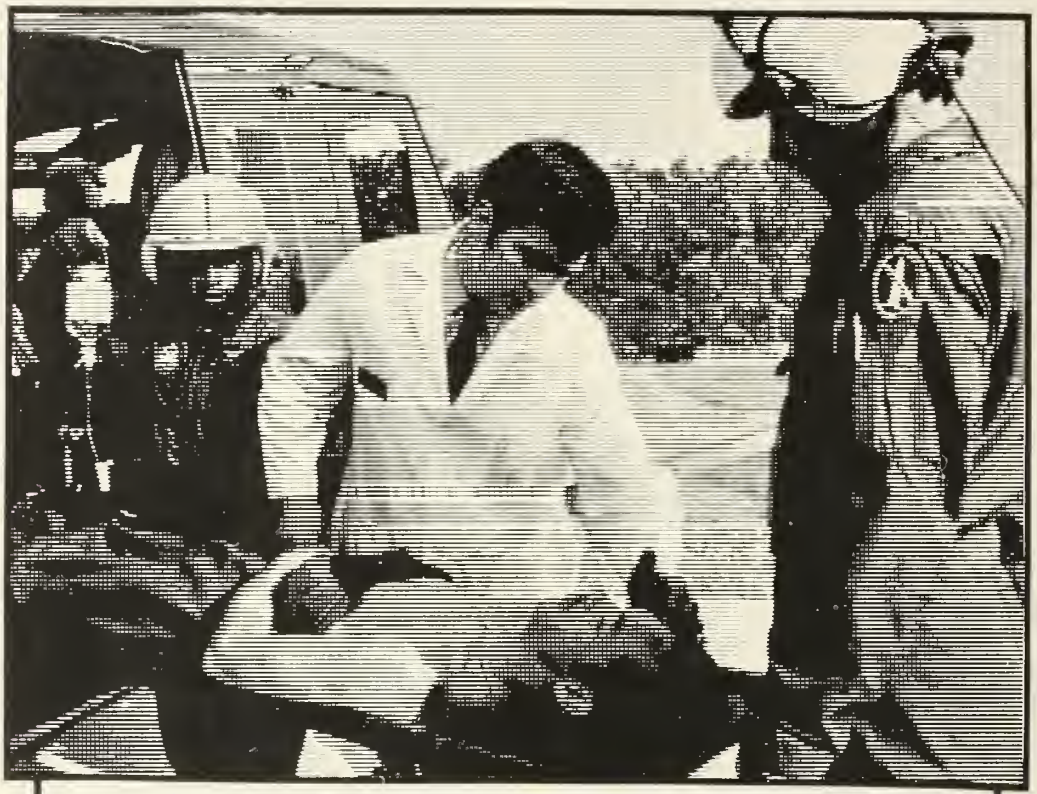
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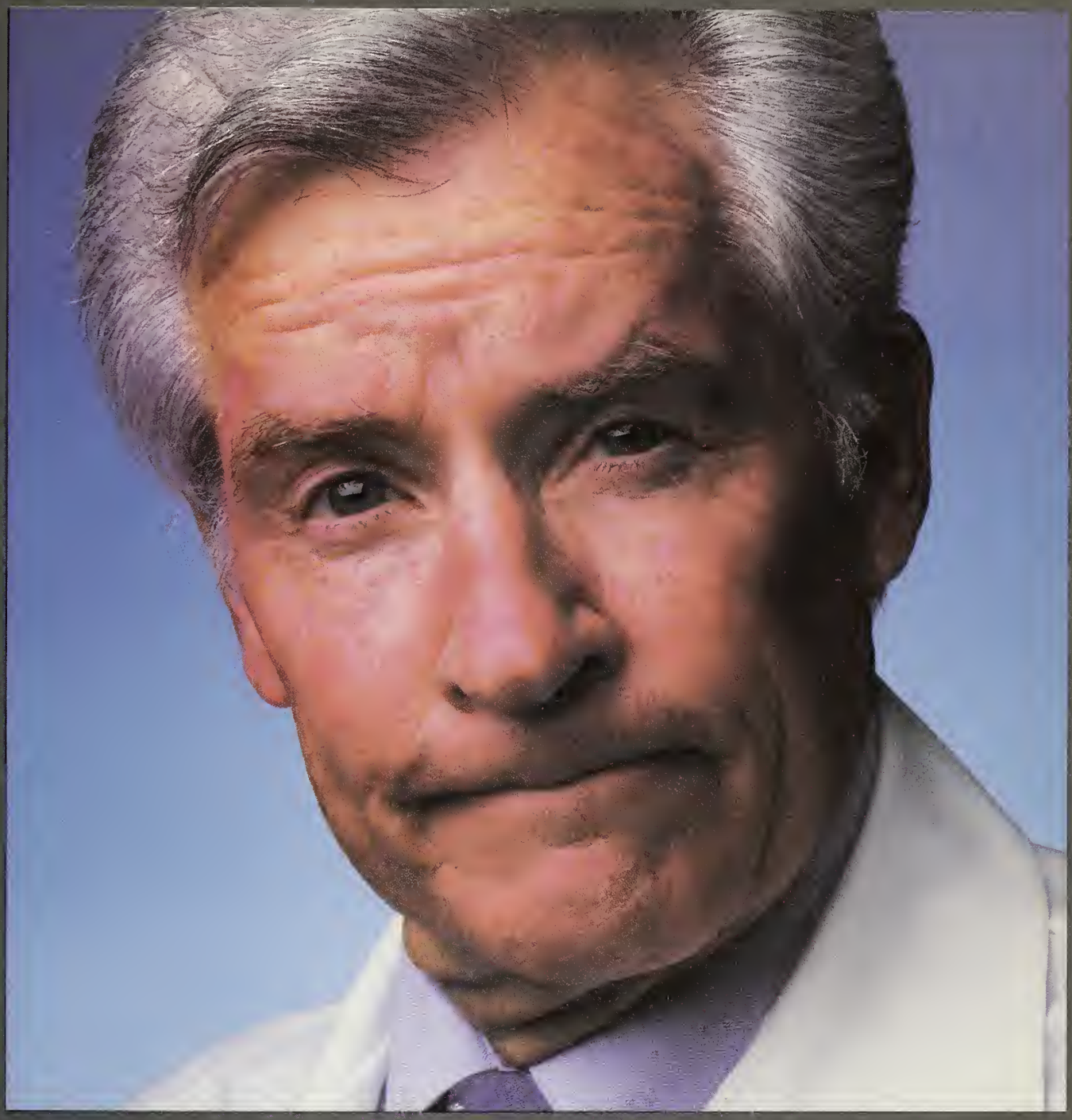


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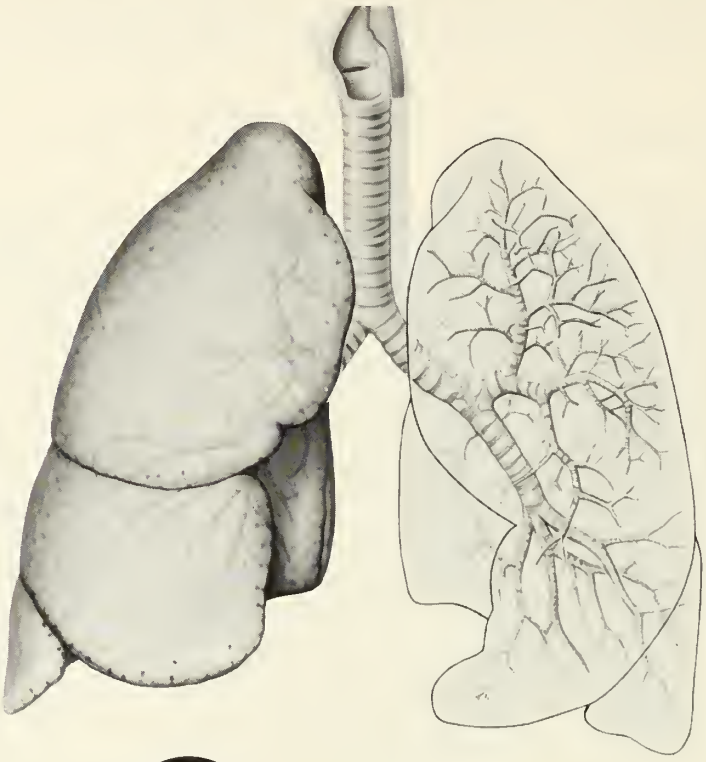
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Indications and Usage. Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae) Haemophilus influenzae* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication. Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings. IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy — *Pregnancy Category B* — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions. Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note. Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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North Carolina Medical Journal

Features for Patients December 1984

Bulimia and Anorexia Nervosa: Dangerous Eating Disorders

Robert T. Harris, M.D.

Eating and proper nutrition are obviously essential to maintain good health. Just like so many other activities that we humans indulge in, however, eating can become a problem if it is done too little or too much. Eating can also become a problem if the substances eaten are harmful or if eating is combined with other potentially harmful activities, like self-induced vomiting. The American Psychiatric Association has defined four eating disorders: bulimia, anorexia nervosa, pica, and rumination disorder.[1]

Eating disorders are becoming more commonly recognized. A recent survey of 300 suburban women shoppers found bulimia in 10%, anorexia nervosa in 1%.[2] On college campuses, surveys have detected bulimia in up to 19% of women and 5% of men.[3] Recent revelations in newspaper, magazine, and television reports of eating disorders affecting certain celebrities (e.g., Cheri Boone, Karen Carpenter and Kathy Rigby McCoy) have brought eating disorders to the public's attention.

Though this article focuses on bulimia, anorexia nervosa is discussed briefly and the two disorders are contrasted. These two disorders share certain features but differ on several points as well (see table 1). Pica — the ingestion of non-nutritive substances like paint, plaster, or clay — and rumination disorder — chronic, involuntary regurgitation of nutritive substances (primarily affecting infants) — are much rarer eating disorders and are not dealt with here. On the other hand, obesity is not an eating disorder but a physical condition that usually results from poor eating/nutritional habits and lack of exercise.

From the Division of General Internal Medicine, Duke University Medical Center, Durham 27710.

Features and Causes of Bulimia

Known alternately as bulimarexia, bulimia nervosa, or the binge-purge syndrome, bulimia is likely the most common eating disorder, although it has been less studied than anorexia nervosa. It is characterized by the episodic but rapid ingestion of large quantities of food in short periods of time. Typically, the patient consumes high-caloric, easily ingested and easily regurgitated foods: a one-half gallon carton of ice cream and/or a full bag of cookies eaten in 30 to 40 minutes is not unusual. The patient then "purges" her/himself by inducing vomiting and then resumes the binge with additional foodstuffs. The entire episode of cyclic binges and purges may continue for several hours. An episode may end with the patient feeling exhausted and falling asleep or with the onset of unpleasant physical sensations, like abdominal pain or sore throat. Alternatively, the episode may be interrupted by some social contact such as someone walking in on the patient in the middle of an episode. Ending an episode in this way is particularly troublesome to bulimic patients, as they strive to conceal their behavior (and "evidence," like large quantities of food) from family and friends.

Bulimic episodes may occur daily (or even more than once daily) or several times a week. A period in which bulimic episodes occur frequently is typically followed by a period of infrequent episodes, or even normal eating behavior, only to have bulimia return days or weeks later. Its episodic nature has prompted the comparison of bulimia and alcoholism. Indeed, the two disorders have several common features:

1. they involve the episodic overindulgence of a substance regarded as normal (or with alcohol, at least socially acceptable) when consumed in moderation;
2. the overindulgence tends to be done in secrecy and the reported amount (of food or alcohol) consumed is minimized;
3. patients are plagued by extreme guilt and feelings of being "out of control" of their behavior;
4. the binges are typically followed by periods of abstinence, only to

have the averindulgent behavior return in days ar weeks;

5. the disarders may be attended by prafaund depression, which may be expressed by the overindulgent behaviar;
6. the disarders carry the patential far a variety of significant, even lethal, medical camplications.[4]

A difference between alcahalism and bulimia is that alcaholism is usually regarded as a disarder affecting men (thaugh the prevalence in wamen is likely higher than generally regarded) whereas bulimia, like anarexia nervasa, appears ta be a disarder much mare cammanly affecting wamen. Female victims af bath disarders have reparted that their bulimia was much more difficult ta cure than their alcahalism, thus underscaring the gender selectivity of the twa disarders. Thus, bulimia and alcahalism can be thaught af as sex-specific expressians of a single indulgence disarder.

Bulimia appears ta share a saciaecanamic feature with anorexia nervosa: both eating disarders are almast exclusively faund in white women fram the middle to the upper saciaeconomic classes. Anather feature shared by bath disorders is the "fear af fatness" cammanly expressed by bulimic and anarexic patients. A clue ta understanding the occurrence af bulimia and anorexia nervasa may be found in epidemiologic data which show that as sacioeconamic status and age (beyand the adalescent years) increase the incidence of obesity decreases among women.[5] The prevalence of obesity is greatest among black women whose family income is below the natianal poverty level. Bath bulimia and anorexia nervosa are exceedingly rare among black women, especially those from lower income families, where obesity is more "the norm" for women, with 49% of poverty-level black women being obese.[5]

The "fear of fatness" found in bulimic and anarexic women may be appreciated better if one considers the wamen who have been established as madels af great beauty, charm, and poise. Over the past fifty years, the winners of the Miss America pageant have became taller while their body weight has decreased on average. The same phenamenan is abserved in the *Playboy* magazine centerfald madels, many af wham weigh less than the calculated ideal bady weight for their height. Yet nane af these "madel" wamen are anarexic in appearance, as being tao thin is generally regarded as unattractive as being taa fat.

Bulimia may seem ta be the perfect answer far wamen wha fear "gaining an ounce af fat" yet want ta remain "normal" in appearance. Many bulimic wamen have faund that they can eat all they want withaut gaining weight. Indeed, the majarity of bulimic wamen are near their ideal bady weight and some are even heavier. This is in sharp contrast ta anarexic patients wha by definitian are at least 25% belaw their narmal weights. Furthermare, anarexic patients take great pride in their thinness and their ability to shun food so cansistently (thaugh same anarexic patients may accasianally binge and purge).

The extreme weight cansciousness and "fear of fatness" shared by bulimic and anarexic patients seems consistent with the fact that nearly 50% of bulimic women have a history of anorexia nervosa.[6] Thus bulimia may develop as a "burned-out" form af anarexia nervosa in patients with an anorexic history. Bulimia "allaws" these women ta maintain their weight consciousness while not appearing anarexic. Bulimia in a previously anorexic woman is viewed as a bad prognostic sign, with bulimia becoming a chronic problem which may continue for many years.

Purging behavior in bulimic patients most commanly takes the form of self-induced vomiting. However, bulimic patients have found other clever ways of purging themselves of the foodstuffs and guilt imposed by their binge eating. Abuse af laxative or diuretic drugs and excessive physical exercise are used by same bulimic patients ta rid themselves af unwanted calaries. Mast bulimic patients are unaware, hawever, that laxatives and diuretics are ineffectual in dispasing af unwanted calaries.[7] Furthermare, when taken frequently or in large quantities (same patients may take up ta 50 laxative tablets a day), these drugs can present dangerous medical prablems. Hypakalemia, ar lawered patassium cantent in the blood, is a camman result of laxative and diuretic abuse. Symptams ranging fram mild muscle cramps and weakness ta fatal cardiac arrhythmias (heart beat irregularities) may result fram hypakalemia.

A number of ather medical prablems can result fram binge eating and self-induced vamiting,[4] even if laxatives ar diuretics are not used. Acute dilatatian (rapid expansian) and even rupture af the stomach have fallawed large binges. Heart failure has develaped in patients wha suddenly embark an a series af binges after a periad of self-impased starvatian. Aspiratian pneumonia, rupture af the esaphagus, hypokalemia and ather metabalic derangements may fallaw frequent vomiting (same patients induce vamiting 35 ta 40 times a day). Even the teeth are not spared, as frequent vomiting erodes the protective enamel of teeth.

Treatment Considerations

Treatment of bulimia begins with the patient wanting help and accepting the fact that her behavior is abnormal and dangerous. Again, one is reminded of alcoholism; treatment of the alcoholic patient is almost impossible until he wants help. Bulimic patients, like alcoholics, may feel such profound guilt for their behavior that "admitting" it to anyone may be an obstacle to treatment. Family members, ministers, teachers, friends, or primary care physicians (rarely psychiatrists initially) may be approached by the bulimic patient. A

Table 1. Comparison of Bulimia and Anorexia Nervosa

	Bulimia	Anorexia Nervosa
Age af Onset	Late adolescence thraugh young adulthaod	Usually mid- ta late adalescence
Bady weight	Variable; near ideal bady weight but may be abave ar belaw	25% less than narmal weight far height
Self-impased starvatian	Seldom a feature	Always a feature
Fears af fatness	Cammanly	Always
Disarder cancealed fram discavery	Always a feature	Rarely a feature; patients take pride in their thinness and ability ta shun faad
Binge-purge behaviar	Always a feature	Occasianally a feature
Medical camplicatians (see text far definitions)	Hypakalemia, paratid enlargement, aspiratian pneumania, esophageal tears, gastric dilatatian, dental erasions	Pratein-calarie malnutritian, amenarrhea, anemia, bradycardia (slaw heart rate), infertility, lanuga (downy hair), heart failure, sleep disarder

sympathetic, non-judgmental attitude by the one approached will facilitate the treatment process by allowing the patient to feel that she has a supportive ally.

The woman must then be referred for evaluation (medically and psychologically), and specific treatment of the eating disorder must begin. Primary care physicians may be the ones to make the diagnosis, possibly even before the patient admits the abnormal behavior. Non-specific complaints of weakness, abdominal discomfort or fatigue may lead the physician to certain physical findings on examination (e.g., parotid gland enlargement or muscle tenderness or weakness) or certain laboratory abnormalities (e.g., hypokalemia) which suggest the diagnosis. Further medical evaluation may be necessary to exclude the presence of other potentially dangerous medical complications of bulimia. The physician should not only treat any medical complications but also be willing to work collaboratively with the therapist treating the abnormal behavior.

Specific treatment of bulimia generally requires a mental health professional (counselor, social worker, psychologist, psychiatric nurse, pastoral counselor, or psychiatrist) with training in treating eating disorders. Behavioral treatment programs may take the form of individual or group therapy and may take place on an inpatient or outpatient basis. In-hospital treatment is necessary if significant medical problems exist or if the patient is profoundly depressed.

Behavioral assessment and treatment of bulimia begins with a baseline study. This consists of asking the patient to keep a diary of her binge-purge behavior. Data to record include the time of occurrence and length of bulimic episodes, the type and quantity of foods ingested, the frequency and methods of self-induced vomiting, the frequency, duration, and type of exercise, the frequency of laxative or diuretic drug use and how the episode ended. The patient is also asked to record her feelings at each point during the bulimic episode, any ideas as to what (if anything) may have triggered an episode and any unusual physical sensations or symptoms during or after the episode. Occasionally patients may find that the mere recording of these data is therapeutic in that it points out the severity of the problem and the need for help.

Further behavioral therapy is aimed at decreasing the frequency of bulimic episodes by imposing an undesirable condition into the episode. For example, the spontaneity and reflex nature of an episode may be countered by planning an episode; such a plan may specify the exact time, length, and place of the bulimic episode, the quantity and types of food to be ingested, and the number of vomiting episodes. The planned binge-purge episode must be carried out exactly as "prescribed" and regardless of whether the patient "feels like it." Another planned episode may be designed to occur in front of a friend or family member, thus removing the secrecy component of bulimia.

Nutritional assessment and education are often included in a treatment program. Bulimic patients may carry a variety of erroneous facts about certain foods with regard to fat or calorie content. A dietician can help design a diet that is nutritionally sound yet respects the patient's continued fear of gaining excess weight. Nutritional counsel can also provide guidelines for food preparation techniques and for handling potentially troubling situations such as shopping or eating at restaurants.

Bulimic patients frequently require psychotherapy which can be combined with behavior therapy by skilled therapists. Psychotherapy helps the patient gain an understanding of how stressful situations may result in bulimic episodes. Psychotherapy may also be needed to treat coexistent depression. Bulimia is considered by some researchers to be a "depressive equivalent" or an atypical expression of depression manifested by the eating disorder.

Indeed, depressian has been diagnased by psychiatric interview and psychalagical tests in a gaad percentage af bulimic patients. Thus one prapased treatment af bulimia is ta treat the underlying depressian. Psychatherapy has been emplayed alang with antidepressant medicatians ta treat depressian. Initial studies of the use af antidepressants are pramising,[8] but more study is needed ta determine if these drugs pravide lang-term benefit in bulimia.

Referral saurces for the evaluatian and treatment af eating disorders, particularly bulimia, may be difficult ta lacate. Primary care physicians, cammunity mental health centers, family caunseling services, practicing caunselars, psychalagists, ar psychiatrists may be lacal saurces ta check far evaluatian and treatment services. Those patients withaut lacal prafessianals praviding treatment far bulimia may wish to contact similar resaurces in a neighbaring, larger caunty ar may cantact ane af the academic medical centers which generally have physicians and behaviar therapists interested in eating disarders. If all af the abave fail, ane af the fallawing agencies may pravide a further list af treatment resaurces: American Anarexia/Bulimia Associatian, phone 201/836-1800; Anarexia Nervasa and Assaciated Disarders, Inc., phane 312/831-3438.

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Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions: *Aspirin*: used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System**: Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses**: Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation, see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System**: Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia, **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit, **Cardiovascular**: Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal**: Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria, **Miscellaneous**: Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System**: Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri, **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses**: Conjunctivitis, diplopia, optic neuritis; **Hematologic**: Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction, **Cardiovascular**: Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic**: Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis: Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

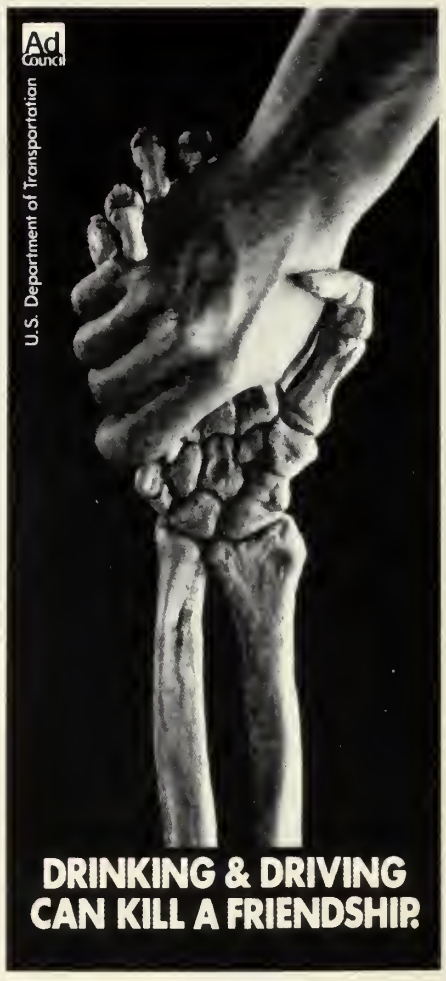
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J-4791 August, 1984



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Dandruff and Seborrheic Dermatitis

Russell W. Eyre, M.D., Claude S. Burton, M.D. and J. Lamar Callaway, M.D.

"Oh, no. He's scratching his head. He must have dandruff." Advertisers have equated bad breath, body odor, and dandruff with social unacceptability. They assure us that just a few short minutes spent each day in the company of their products will assure us all of an active social life and plenty of friends.

Everyone has dandruff to some degree. We all shed our skin every forty-five days. People with dandruff just shed their skin at a faster rate and in larger, visible, clumps of cells. Each square inch of a normal scalp sheds about 70,000 cells a day. Scalps with dandruff shed twice this amount. Individual cells that are shed are much too small to be seen with the unaided eye. They're invisible. However, in dandruff these cells don't fall off individually. Bonds that normally break and allow cells to be shed singly hold fast. The result is the familiar snowflake scale of dandruff.

When inflammation or redness occurs with dandruff the diagnosis is usually seborrheic dermatitis. This is one of the most common skin diseases seen by the dermatologist. From two to four of every hundred people have some form of seborrheic dermatitis. The term seborrhea comes from the Latin, sebum, which means tallow or lard, and the Greek, rhoia, which means to flow. Seborrheic dermatitis refers to an eruption that occurs in those areas of the body rich in oil, or sebaceous glands. These glands are abundant on the scalp, face and central chest. Patients with seborrheic dermatitis often have a glistening or shiny appearance to their scalp and symmetrically distributed orange-yellow scaling patches. These patches are most commonly found scattered over the scalp, along the scalp margin, in the eyebrows and eyelashes, over the central chest, in the ears, along the sides of the nose, and in the nasolabial fold.

The cause of seborrheic dermatitis is unknown. Stress, overwork, and infrequent shampooing may worsen the dermatitis. During both World Wars great numbers of troops were affected and some were even incapacitated by secondary infections of their dermatitis. It is not uncommon for a patient who has just had a heart attack to also experience an attack of seborrheic dermatitis. Students at examination time often experience increased scaliness. Infants and adolescents are commonly affected with sebarrheic dermatitis; the sebaceous glands are very active at these times. Patients with Parkinson's disease (a neurological disorder) and patients with spinal cord injuries (especially quadraplegics) frequently have severe seborrhea even when they shampoo often. Treatment of Parkinson's patients with L-dopa, a chemical they lack, usually improves their seborrheic dermatitis.

It was thought that because many of the conditions associated with the dermatitis are also associated with an abnormality of sebaceous gland activity that the sebum must play some role in causing the dermatitis. However, the greasy appearance is not due to increased amounts of sebum produced. The sebum is just trapped in the abundant scales. There is an increased proportion of free fatty acids in the sebum but these acids are secondary to increased amounts of bacteria that digest triglycerides into free fatty acids. The increased bacteria are probably also just trapped in the scales because even if the bacteria are killed with antibiotics the dermatitis remains. Yeasts, especially Pityrosporum ovale, have been implicated as a cause of sebarrheic dermatitis. There are increased numbers of these micro-organisms on the scalps of patients with sebarrheic dermatitis but normal scalps have these yeasts as resident flora, and treatment that reduces the number of these yeasts does not necessarily improve the dermatitis.

Psoriasis may be confused with sebarrheic dermatitis but the scales of psoriasis are generally thicker and occasionally the underlying scalp bleeds when the scales are removed. Besides the scalp, psoriasis is found mostly over joint surfaces while sebarrheic dermatitis is distributed in body folds. Sometimes it may be impossible to distinguish between psoriasis and seborrheic dermatitis. A hybrid term, "sebapsorias," has been coined to describe this condition. Ringworm of the scalp may also mimic sebarrheic dermatitis. The correct diagnosis is made by examining the scales under a microscope or culturing them. Usually there is hair loss with a fungal infection of the scalp while hair loss is not a feature of dandruff, seborrheic dermatitis or psoriasis.

No one except "Dr. Guillotine" ever cured seborrheic dermatitis. It is a lifelong condition marked by remissions and exacerbations. There are several effective treatments available which if used regularly will diminish the scale to invisible levels. Rarely a drug such as cimetidine, chlorpramazine, gold, or arsenic causes seborrheic dermatitis. Stopping the drug will cure the dermatitis.

The first choice of treatment is an anti-dandruff shampoo. There are several types available. One type contains chemicals that help to break the bonds that hold scales together. These kerotalytic, scale dissolving agents, such as sulfur and salicyclic acid, are found in Sebulex, Ionil, and Vanseb. Shampoos that inhibit rapidly proliferating epidermis such as Selsun Blue, Exsel, Zincon, Head and Shoulders, and Dannex are also effective. However, those that con-

toin selenium moy couse diffuse hoir thinning especially if used for long periods of time. Tor shompoos such os Ionil-T, Sebutone, Vonseb-T, Zetor, and T-gel decrease inflammation and ore becoming more cosmeticolly acceptable. When thick scoles are present the overnight application of an oil or greose moy help to loosen the scales. We recommend olive oil, moyonnaise, voseline, boby oil, Baker's P ond S, or Dermasmoothe FS.

Seborrheic dermatitis is extremely responsive to steroids. In the scalp, stronger steroid solutions such os Syunalar, Valisone, Diprosone, or Lidex moy be used intermittently. On the face or chest, only milder steroids should be used to avoid complicotions such os adult acne, stretch morks and thinning of the skin. We use 1% hydrocortisone, Westcort, Tridesilon, or Hytone. On the eyelids Blephomide solution which contoins sulfur ond a mild steroid is effective but the potient should be followed by on ophthalmologist to monitor steroid side-effects in the eye such as cotorocts and gloucomo. One otolaryngologist collects ear wox removed from normal patients ond resuspends it in o glycerin solution which he dispenses for seborrheic dermatitis of the eor conol. If the dermotitis becomes secondarily infected o course of orol ontibiotics moy be required.

With proper core ond dermotologic consultotion oll but the most difficult patients may be rendered free of dandruff and oble to wear dork sweoters without feor of sociol emborrossment or snowflokes on the shoulders.

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'Tis The Season To Do Folly: Horrendous Holiday Horticultural Happenings

Ronald B. Mack, M.D.

• *This is a good time to remind you that many lovely Christmas plants are toxic. Little people are especially attracted to their bright berries and leaves — an attraction with potentially fatal consequences.*

I would suspect that most people look forward to the Christmas-New Year season with great joy. To the health care professional involved in emergency care, however, this time of year is coated not with tinsel, but with a small amount of dread. Bah humbug, you exclaim! Just think of it, how many situations during the Holidays can you name that portend potential disaster for the wee folk for whom Christmas is the event of the year.

Accidents increase in children whenever there is a change in routine, e.g., during vacations, house renovation, illness or death in the family, birth of a sibling, just to name a few. This being the case, the holiday season brings an incredible number of changes for the young investigator-taster such as an increase in *visitors* (and their medicines), an increase in *visits* (to homes with many, many "goodies" to sample including cookies; cakes; household cleaning, polishing and sanitizing agents; medicines; etc). Remember that Grandma's house is one of the most dangerous sites in a pre-school child's environment, accident-wise, particularly involving drugs of a cardiovascular nature such as digitalis compounds, antihypertensives, cardiac rhythm regulators, etc. What about the visits to one's father or mother who no longer shares the family home because of separation or divorce; plenty of opportunity there to get into potential toxins now that the dwelling no longer is "poison proof" on a continuous basis. The season brings with it a sharing of gifts — lots of new stuff entering the house — Christmas tree; ornaments; tinsel; toys to swallow and stick in your eyes, ears, nose or throat, or other orifices that I would rather not mention; plants of the holiday season and of course, in many homes, more alcoholic beverages on display, ready for dispensing to visitors or self. Gosh, but it's scary to think of all this — notify the Grinch and call the whole darn Holiday off — it does not seem to be worth it. Do you recall what Ebenezer Scrooge said in Charles Dickens' classic *The Christmas Carol:* "out upon Merry Christmas! What's Christmas-time to you but a time for paying bills without money; a time for finding yourself a year older, but not an hour richer. . . . If I could work my will, every idiot who goes about with Merry Christmas on his lips should be boiled with his own pudding and buried with a stake of holly through his heart."



One area of toxicology that does seem to increase in the Joyous Season is the ingestion of plant material indigenous

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

Illustrations by Ernest Craige, M.D.

to the holidays. Therefore, I am submitting these words to those health care practitioners out there in the real world who may be confronted with people, big and small, who ingest berries, leaves, flowers, stems of holiday plants.

Poinsettia: The poinsettia was introduced in the United States in 1828 by Joel R. Poinsett, then U.S. Ambassador to Mexico. This plant, one of the most typical symbols of the Yuletide, suffers from bad public relations. Every Christmas the debate resumes about this beautiful plant's toxicity; the complete answer is still not in. However, a reasonable judgment concerning its potential dangers can be made on the basis of its history. Yes, I know that the literature says that in 1919 a child in Hawaii died after eating poinsettia leaves. So what, must the plant be maligned forever? The plant has been punished enough. During those same years one of my Dad's cousins blew away a competitor during the Prohibition territory wars and he was forgiven by a sympathetic judge in Chicago (the best that money could buy). The plant that killed the child in Hawaii was alleged to be an indigenous wild poinsettia plant. The modern day plant is a hybrid with properties considered by most authorities to be non-lethal. Now it is true that the plant contains a milky, white sap in the leaves, stems and flowers (AKA bracts) and this sap can be very irritating to the eyes, skin and gastrointestinal tract. In susceptible individuals an acute contact dermatitis can occur from contact with the sap but this event is not common. Ingestion of the leaves or red bracts can cause vomiting, diarrhea and abdominal pain. The leaves are quite bitter and most little people probably would not swallow them in quantity.

A few years ago one of my sons, at a fraternity Christmas party, allegedly consumed two poinsettia leaves as an act of bravado to impress his fraternity brothers and assorted lady friends. It is alleged by competent (?) witnesses (some of whom were alleged to be acutely mind-altered at the time) that there were no sequellae following this ingestion. My son did not tell me about this impromptu experiment until a year later. After all, he does not know what I do for a living, do any of your children really know what your work consists of? The funny thing is — like most of our own younguns — he never listened too well to parental requests; if I would have asked him to swallow the leaves as a research project for me he probably would not have done so.

In the recent literature there is an article[1] describing an infant who chewed on a poinsettia leaf and acquired burns of the buccal mucosa. I suspect this phenomenon is not very common, but should be noted. The treatment is symptomatic if the patient gets involved with this plant. Gastric decontamination is probably indicated if the patient has not vomited already.

Mistletoe: This bit of flora conjures up warm feelings of closeness that are such a part of the Season; it makes us think of the kisses that you gave or received while standing under this plant or the kisses you wished you had given or received. However, mistletoe is a bad actor, poison-wise. We should have been able to predict its evil behavior — in Norse mythology, the mistletoe was the only living thing that did not swear an oath not to harm the great Balder (remember him?) who was the god of beauty and light. Balder was the son of Odin, the number one Norse god. Loki, a feared enemy of the god, slew Balder with an arrow made of mistletoe. Heaven forfend — I never knew anyone who died as a result of mistletoe but I did know an intern mate of mine who got the stove-top stuffing beat out of him



for kissing a nurse (who was betrothed to another) while both happened to be under the mistletoe.

The mistletoe is really nothing but a parasite — literally. This plant is a parasite of the oak and other trees and contains two amines that are potentially very toxic indeed — tyramine and beta-phenylethylamine — and ingestion *can be fatal*. All parts of the plant contain these amines, but it seems to me that small children would be most attracted to the berries which are pea-sized and fleshy white. These toxic amines stimulate smooth muscle resulting in hypertension, bradycardia and increased uterine and intestinal motility. The poisoned patient can experience nausea, vomiting, diarrhea and severe abdominal pain. The most severe and therefore potentially lethal consequences of mistletoe ingestion relate to the cardiovascular system, i.e., vasoconstriction and cardiac arrest; delerium and hallucinations and seizures can also occur. Animal studies have shown that the amines from the mistletoe plant produce the same effects as an injection of the cardiotoxin from cobra venom. Mistletoe extracts are sold in health food stores as it is one of the oldest and most widely used herbal remedies. It has been recommended by "nature lovers" as a treatment for asthma, epilepsy, pregnancy (has been used historically as an abortifacient), infertility as well as an aphrodisiac (it doesn't work). In a recent report in the British literature,[2] mistletoe tea ingestion was thought to be responsible for a case of hepatitis.

Remember that this plant can kill if ingested — early gastric decontamination is certainly indicated even if the child only ingested a few berries (more than 1 or 2 or 3?, how can you tell if the history is accurate? Protect the patient and yourself). Monitor the patient's cardiac status and potassium status as you would a patient who ingested digitalis-like drugs.

Christmas Holly Berries: No question about it, holly berries look good enough to eat and people do. The bright red berries (some are black) are so attractive that some children find them hard to resist but they can result in poisoning, sometimes very serious indeed — including death. Holly trees grow up as either male or females (isn't that sweet); therefore only half the trees bear the poisonous fruit and I can't figure out which half — oh well, that's my problem. Are there trees that can go either way? (Hush boy, this is a family magazine.)

Ingestion of the leaves (rare because they have many sharp spicules) or most particularly the berries can result in almost immediate mild to severe nausea, vomiting, diarrhea and abdominal pain. The loss of fluid can be so remarkable as to produce serious fluid balance problems. Some authors claim that holly berry ingestion can cause CNS depression including coma and death but the data are soft. The exact toxin contained in the holly is not that well defined but some authors state that the culprits are theobromine, saponins and triterpenes. It seems that children are particularly sensitive to the irritant gastrointestinal action of the saponins. Apparently small amounts of the toxin contained in the holly berries can stimulate the CNS but large doses act as depressants. If a child ingests more than 2 or 3 berries it is probably helpful to empty the stomach and administer charcoal. It is not necessary to induce emesis if the patient has already vomited enough to empty the stomach. It has been estimated that the ingestion of 20-30 berries may be fatal to a small child.

Jerusalem Cherry: This beautiful decorative plant with abundant red or yellow cherry-sized fruits is especially popular around the Christmas Season. The fruit can resemble those delectable small cherry tomatoes that all real salad-lovers crave. Do not be misled, these wonderful looking things are potentially very toxic to an unwary ingester. Both the leaves and bright berries are considered very poisonous. The toxin contained in the berries is a *solanine*, specifically solancapsine which is a toxic glycoalkaloid. Relatively small doses of solanine are very irritating to the GI tract causing vomiting, diarrhea and abdominal pain. The initial adverse clinical feature is an irritation of the oral mucosa and a scratchy throat. Large doses can result in respiratory distress, bradycardia, cardiac depression, cardiovascular collapse and even death. Some patients experience mydriasis, fever, confusion, dizziness and excessive salivation. Death is rare but has been reported. Some people make a jelly from the cooked ripe berries; no thank you. I prefer Smuckers, in spite of the name. The treatment is standard and symptomatic. If the patient has not vomited, induce emesis and administer activated charcoal. Some patients act as if they have been poisoned by atropine and should be managed accordingly.

It seems reasonable to suggest to parents who seek guidance for a child who has ingested a poisonous plant to suggest that the mouth be washed out with water and then to administer ipecac syrup if all the proper conditions are met. The administration of activated charcoal appears to be quite helpful in the management of poisonous plant ingestions.

What can we learn from all of this? Eliminate the Holidays — no festive plants, no gifts, nothing or at best give children an orange in their Christmas stocking and bad children lumps of coal. By the time I was eight years old I had accumulated enough coal to heat Cleveland for a week.

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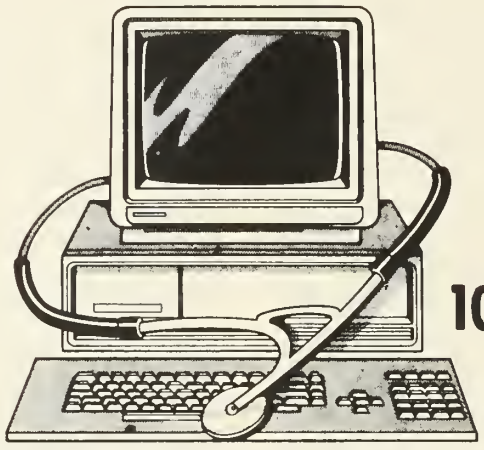
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An Account of How Deep Hypothermia Was First Used to Increase the Safety of Open Heart Surgery

Will C. Sealy, M.D.

• *How a five-year-old "blue baby" girl in the right place at the right time lived to grow up and produce her own healthy children.*

TWENTY-FOUR years ago, a five-year-old girl, blue, breathless, and having frequent falling out spells, was brought to Duke Hospital seeking help. A series of examinations showed that her illness was caused by two heart defects, one a partial blockage of the vessel connecting the heart and lungs, and the other a large hole between the two ventricles. This caused the volume of venous blood circulating in the lungs to be reduced and shunted to the left ventricle, markedly diluting the arterial blood, resulting in her life-threatening problems. The patient was a "blue baby" and her heart disease was called the Tetralogy of Fallot. After careful review of all examinations, the decision was made that the best and safest treatment would be to open her heart and correct the defects, rather than to do a shunt operation that would only partially relieve her symptoms for a short time. This decision was influenced by the recent development by the Duke cardiac surgeons of a new method for opening the heart using deep hypothermia controlled with a pump oxygenator. This is an account of how this new method, a landmark event in open heart surgery, was devised at Duke and then used in its first clinical application to cure this sick child of her congenital cyanotic heart disease.

In the mid 1950s, open heart surgery could only be done using one of two methods. The first,[1] surface-induced mild hypothermia (temperatures in the esophagus of 32-34°C) used alone, allowed only five to seven minutes of open heart time, since the circulation had to be stopped in order to open the heart. The second,[2] utilizing the heart-lung machine, allowed about thirty minutes of safe time to work within the heart. In 1954, when I began to consider these two methods, neither of the two appealed to me as being safe or practical. It seemed logical, however, that the two methods, when combined, would give the advantages of both, although no other surgeons at that time were deliberately doing this. My reasoning was that the mild hypothermia would reduce the oxygen demand as well as other metabolic requirements to the point where a low-flow perfusion by the then available heart-lung machines would supply the needs.

In using the combination of mild hypothermia and extracorporeal circulation at Duke,[3] the patient's temperature was reduced to about 32°C (90°F) by immersion in a tub of ice water. This required 60 to 90 minutes. Next, the patient was connected to a pump and bubble oxygenator using flows of about 2500 cc for an adult. The open heart operation was then done. When the operation was completed, the patient was disconnected from the heart-lung machine and rewarmed with hot water bottles or immersion again in a tub, but mostly this occurred with heat generated by the patient's own metabolic activity, an added stress to an ill patient. Although this new method was still time limited, it afforded us a practical and safe method for correcting most simple congenital cardiac defects.

As the members of the cardiac surgical team watched the patients during the long rewarming process, the obvious solution to this awkward and dangerous step soon became evident: Use the heart-lung machine to rewarm the patient. The first attempts to do this were with the plastic tubing added to the arterial line of the pump, passing the extra tubing through a trough of warm water. This failed. The thick plastic tubing was grossly inefficient as a heat exchanger. This problem was solved by Ivan Brown, Wirt Smith and Allan Lesage. Wirt Smith had a background in engineering and was then a fellow with Ivan Brown in the Duke blood bank. Allan Lesage ran the thoracic surgical laboratory and operated the heart-lung machine. Long thin stainless steel tubes replaced the plastic ones. These were satisfactory. Once we established that warming could be easily done, the next step also became obvious: Cool the patient by allowing the blood entering the patient to pass through steel tubes immersed in cold water. This handmade device was efficient and gentle on the blood, and marked the first time a heat exchanger had ever been used with a pump oxygenator. The method is called core cooling in contrast to surface cooling that occurs with immersion.

The next episode in this story illustrates what a large role

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luck can play in solving a surgical problem. At the time we found we could regulate temperature during heart-lung bypass with a crude heat exchanger, it was close to the Christmas holidays. Ivan Brown's family lived in Lockport, New York, a town close to the Harrison Radiator Division of General Motors. While visiting his family over the holidays, Ivan met Mr. W. D. Emmons, the Chief Engineer at Harrison. Ivan, who was one of this country's leading authorities on blood banking, seized this unique opportunity. With engineering capability of one and blood handling knowledge of the other, an efficient heat exchanger for a heart-lung machine was planned and then fabricated.[4] The instrument consisted of multiple highly polished stainless steel tubes for blood transport, surrounded by a water jacket for circulating water. The heat exchanger had to be extremely efficient to be practical. On an adult at the flow rates of 2500 ml per minute the perfusion was about half that employed for a 70 kg adult today. With high perfusion rates, even a crude heat exchanger will work. With this machine placed in the arterial line, the temperature of the blood was regulated by water circulating in the jacket at a controlled temperature (figure 1). A modification of this instrument is now part of all heart-lung machines, functioning not only to induce and revert hypothermia, but to maintain temperature at normal levels, even to raise it to hyperthermic levels in certain special situations.

One problem among the many that we were concerned about was the likelihood of the heart developing ventricular fibrillation when made cold. At that time there were no manufactured devices for correcting this arrhythmia, only locally fabricated paddles plugged directly into the 120 volt lighting system. This anticipated problem with the heart was discussed with Jerome Harris, Duke's Pediatric Cardiologist. On his advice, Glenn Young, Doris Merritt and I worked out a heart stopping (cardioplegic) solution containing potassium, magnesium and prostigmine, that would effectively revert ventricular fibrillation.[5, 6] The laboratory studies were completed before we were aware of Melrose's experiments.[7]

In addition to controlling the arrhythmia, cardioplegia was found to permit cross-clamping of the aorta and thus interrupting the coronary blood flow for a short time, because lack of muscle contraction as well as the hypothermia reduced the metabolic demands of the heart. With this method, an intracardiac operation could be done, in part, in a relatively dry field.

With our low flow bubble oxygenator and mild core-induced hypothermia and cardioplegia, a large group of patients was successfully operated upon. This was reported before the Southern Surgical Association,[8] and marked the first account where these three modalities were deliberately and knowingly combined.

Following our success with the use of the heat exchanger to attain mild hypothermia, logically the next step was the extension of the limits to profound hypothermic levels (below 18°C), which we had good reason to believe would increase the safety of the pump oxygenator, allow more

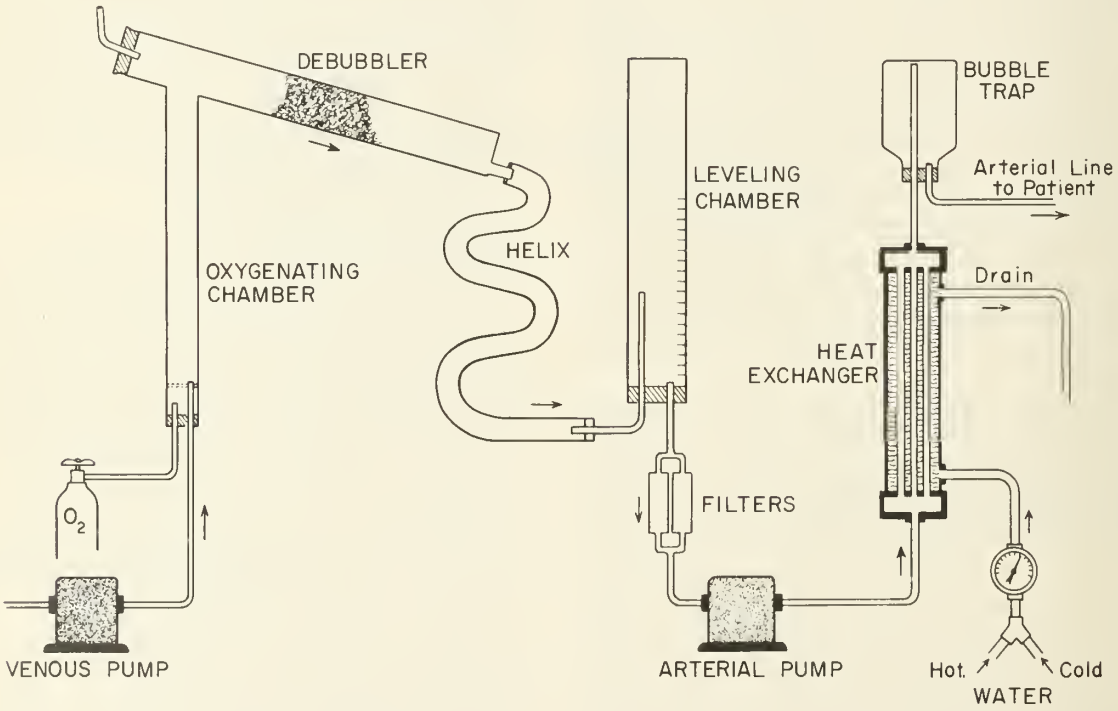


Figure 1. *This is a drawing of the extracorporeal system used for core induction for both mild and profound hypothermia. In large individuals, two heat exchangers were placed in series for the latter. In mild and moderate hypothermia, water from the hot and cold water lines was used, passed through a mixing valve. For deep hypothermia, a large bucket of ice water and a small pump were placed on the system. The oxygenator was fabricated from dairy equipment. The de-bubbler was a Tuffy sponge sprayed with defoaming material. Nearly all currently used oxygenators are modifications of this system, the original DeWall-Lillehei oxygenator.*

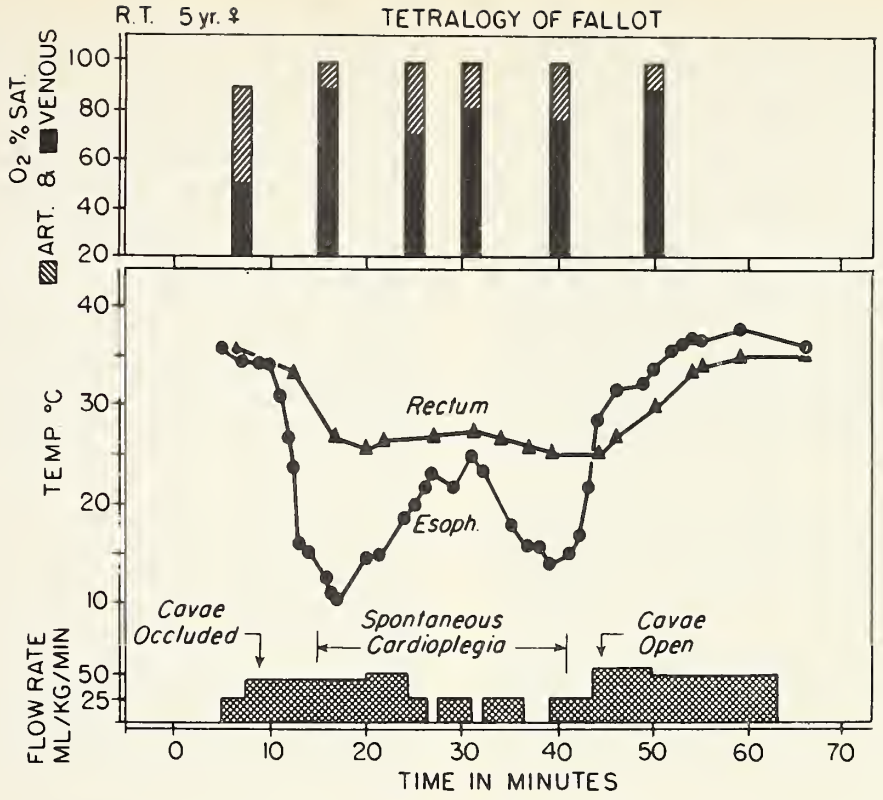


Figure 2. *A record made from observations at operation in the patient described in the text. In the panel above are the percent saturation of samples of arterial and venous blood. In the lower panel, rectal and esophageal temperatures are plotted. There were three short periods of circulatory arrest, as shown in the lower panel. In many patients during deep hypothermia, the heart either went into standstill or into ventricular fibrillation and then standstill.*

time to correct complicated intracardiac problems and, in special situations, allow periods of circulatory arrest but with perfusion continuing for most of the operation. Allan Lesage and various laboratory Fellows from thoracic surgery, many from Japan, carried out hundreds of experiments proving the validity of using profound hypothermia.[9] Among their many observations, they noted temperature differences in various organs, oxygen consumption, acid base balance, tolerance of the cold heart to ischemia, and the times of tolerable circulatory arrest at temperatures below 18°C. In these studies, circulatory arrest during deep hypothermia was found to be safe for 30 minutes and up to an hour with increased risk, the brain, of course, being the most sensitive indicator. Using this laboratory information, as well as our experience with mild perfusion-controlled hypothermia in patients, we then felt justified in the use of deep hypothermia for complex intracardiac operations. Tetralogy of Fallot, at that time, was the greatest challenge in open heart surgery. It was a time consuming, high risk procedure with a high morbidity rate from heart block if hurried and working in the heart in a pool of blood. One clinic reported a 32 percent mortality rate in a cyanotic group of patients with Tetralogy of Fallot.[10]

Glenn Young was the surgeon of the five-year-old seriously ill child with Tetralogy of Fallot noted in the introduction. She underwent closure of the ventricular defect and removal of the pulmonary obstruction using an oxygenator, pump and heat exchanger as shown in figure 1. Her body temperature (as measured in the esophagus) was reduced to 7°C, and three periods of circulatory arrest were used, so that the sutures to close the defect in the septum could be correctly placed avoiding the His bundle and thus preserving atrioventricular conduction. In figure 2, the periods of circulatory arrest are shown, as well as the marked decrease in oxygen utilization demonstrated by the narrowing of the arteriovenous oxygen differences. Note that for the most part perfusion continued throughout the operation. No problem occurred in the immediate or late postoperative period. The patient has led a normal life since the operation and is the mother of two normal children. Following this first operation, fifty additional patients were operated upon.[11]

About this same time, other surgeons, particularly Drew[12] at Westminster Hospital in London, were using profound hypothermia to insure the safety of open heart surgery. Although he used perfusion induced cold, his method was cumbersome. It required two cannulae in the right and two in the left side of the circulatory system, with a second pump to perfuse the lungs which oxygenated the blood, since there was no oxygenator in his system. Circulatory arrest was mandatory for an intracardiac operation. The report from Bjork's[13] experience with the Drew

method where a high percentage of patients had brain damage confirmed the dangers of circulatory arrest for long periods. Bjork's report was influential in curbing the interest in deep hypothermia at that time, even though he did not use what is now the accepted technique.

The Duke neurosurgeons became interested in deep hypothermia as a method of circulatory arrest for easing the problem of exposure to difficult neoplastic and vascular lesions. This first application in neurosurgery was by Barnes Woodhall and the author.[14] The record from one of these patients is shown in figure 3. The measurements of brain temperature made during these operations emphasized the important fact that the brain cooled more slowly than the esophagus. This may have been a factor in some of the early adverse reports about deep hypothermia and circulatory arrest, the latter occurring before the brain was cooled to safe levels.

The recognition of the importance of our studies came when the author was invited to be one of three principal speakers at an international symposium on hypothermia sponsored by the University of Paris and held in 1961 in Paris at UNESCO.[15]

Following our successes in the late 1950s, this method was abandoned at Duke and nearly every other clinic in the United States, only to be revised and returned to use in the late 1960s and early 1970s, due to the efforts of Mohri, now of Japan, who was working at that time with Al Merendino in Seattle.[16] Their method, similar to our early method for mild hypothermia,[8] was to use 18°C. The operation, however, was done with the circulation interrupted. The pump oxygenator was used to rewarm the patient. Soon this technique was abandoned by most and core cooling substituted, just as we had originally advised.[17]

There were several reasons for the temporary abandonment of deep hypothermia for open heart surgery. In our early reports we recommended esophageal temperatures of 7 to 10°C. Now we know that this was lower than needed, and the metabolic gains from this temperature did not compensate for the time needed to reach this level. For example, the attainment of temperature drops from 17°C to 7°C required a much longer time than reducing the esophageal temperature from 37° to 17°C, due to the restrictions of the temperature levels of the water in the heat exchanger acting as the coolant. About this same time, pump oxygenators became more efficient and thus one of the reasons for using hypothermia was no longer as important as it once was. The use of immersion-induced hypothermia by Mohri and Merendino had the great advantage of more uniform cooling of all structures and avoided the slow rate of cooling of the brain which was an unrecognized problem with others who used core cooling. The surgeon did not delay circulatory arrest long enough to allow the brain to cool as shown in figure 3. The 18° to 20°C esophageal temperature can occur well before the brain is cool enough to allow circulatory arrest or, as needed in special cases, interruption of the blood flow to the brain. Just as happened in our initial experience with mild surface-induced hypothermia, core cooling and rewarming with the

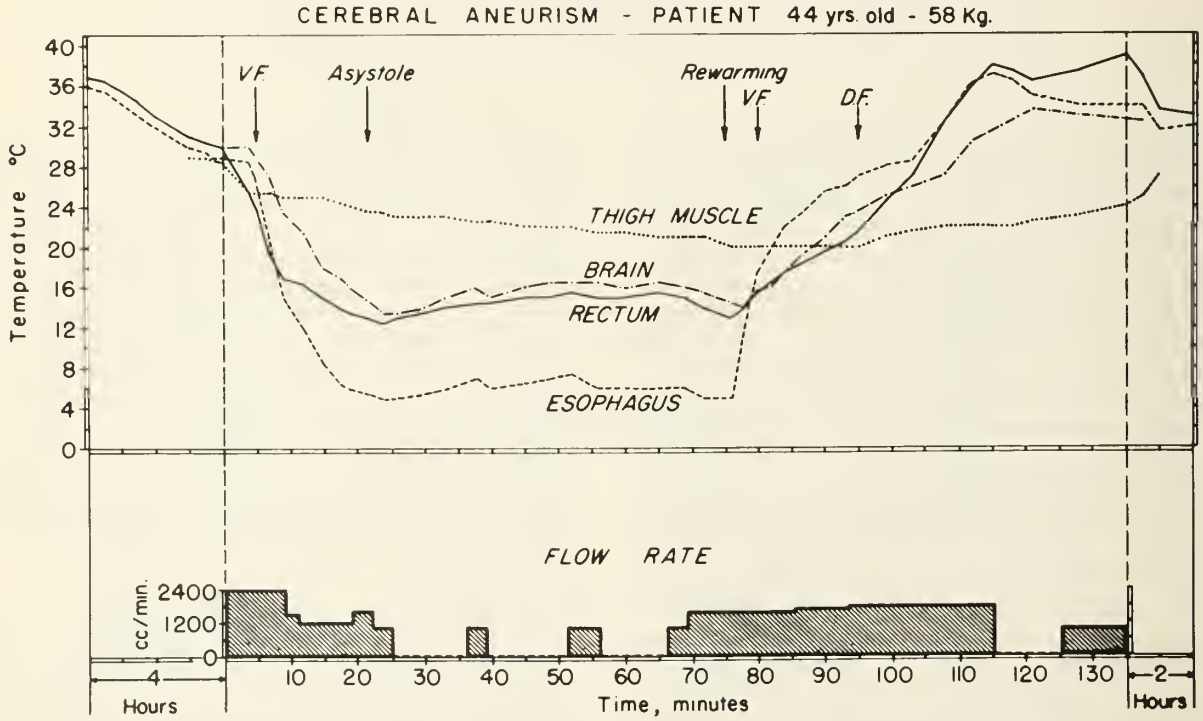


Figure 3. *This is the record made from a neurosurgical patient operated upon for a cerebral aneurysm by Barnes Woodhall. The temperature gradients shown in the upper panel emphasize the lag in the cooling rate of the brain as compared with the esophagus. Note the cooling and rewarming curve of the muscles of the thigh. The lag reflects to a great degree the difference in the rate of blood flow between muscle and other areas recorded. The flow rates and periods of circulatory arrest are shown in the lower panel. VF, ventricular fibrillation. DF, defibrillated.*

pump oxygenator were soon almost universally employed, not only in children but in many adult operations. During deep hypothermia, only a small flow rate is required.

The account of this series of events merits attention for two reasons. First, the story is a landmark event in the evolution of methods that have increased the safety of cardiopulmonary bypass and thus open heart operations. To me, the second is the most interesting. A group of doctors with free communication and mutual respect pooled their various talents and accomplished what turned out to be a paradigm of surgical research, that is, the taking of information accumulated by more basic investigators and, after careful laboratory testing of the applications of these basic principles, applying them to establish new and improved methods of treatment that were a major factor in making heart surgery safe.

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A Report on the Use of a Family Nurse Practitioner to Reduce Industrial Health Care Costs

C. J. Dellinger, M.D., Judy L. Zentner, F.N.T.C., and Wayne Annas

• *A furniture company hired a family nurse practitioner to perform tests, counsel employees, care for minor on-the-job injuries. The results, in dollars and cents, are presented here.*

IN 1982 a local furniture company employing 700 persons was struggling with spiraling health care costs as were other industries across the nation. Its approach to reduce health care costs was a novel experiment, the results of which are reported here.

The company was required by OSHA to check audiograms annually, necessitating the employment of trained personnel. It decided to use a Family Nurse Practitioner (FNP) to do the audiograms plus health screening and review of daily illness and injury situations.

Method

The tasks delegated to the FNP were submitted on her application to the State Board of Medical Examiners. They fell into four areas: 1) audiometry and dosimeter studies for noise exposure, 2) on-the-job emergencies, 3) preventive measures, and 4) health care counseling. She was required to keep medical records which were reviewed weekly by the sponsoring physician.

Audiometry testing had previously been performed under contract by an outside firm. In the period studied, the FNP performed 450 studies. Dosimeter studies involved the documentation of noise levels in different work areas.

On-the-job injuries were seen first by the FNP whenever possible. These consisted of sprains, lacerations, back strains, splinters, and foreign bodies in eyes. During the study period, 800 such encounters were reported. These encounters sometimes included multiple visits by the same persons. Surgical problems were referred directly to a general surgeon bypassing the hospital emergency room and its added expense.

Preventive medicine included updating tetanus toxoid immunizations, flu vaccines, pre-employment physical exams, and annual multiphasic testing.

Health care counseling involved dealing with problems the employees encountered such as upper respiratory infections, urinary tract infections, high blood pressure, marital problems, and alcohol problems. Throat cultures were performed when needed on persons complaining of sore throat. The results were reported to the employee and his or her physician. If the employees were patients of the sponsoring physician, the FNP treated the patient according to the protocol outlined in *Patient Care Guidelines for Nurse Practitioners*.[1] Employees who had other physicians were referred to their own physician for treatment. Urinary tract infections were treated the same way. Conditions such as consistently elevated blood pressure, diabetes, anemia, hematuria, hernias, and thyroid nodules required referral to a physician.

Results

The results of one year's experience are listed in table 1.

The audiometry testing was valued at $8.00 per test by a health testing firm in its contract. Having the Family Nurse Practitioner perform 450 tests represented a saving of $3600. Dosimeter was also valued at $8.00 by outside contractors, a saving of $160 on the 20 measurements.

The possibly-job-related encounters represented 800 visits by employees, including repeat visits. Eye complaints accounted for 100 visits. The largest number of visits was for musculoskeletal complaints, such as sprains and backaches. Trauma and counseling or education accounted for 150 visits each. Sutures were removed from eight persons who had had lacerations repaired. Two minor lacerations were repaired with steristrips.

Preventive maintenance activities accounted for 671 visits.

The largest group of encounters was for health care counseling which accounted for 2330 visits. These visits were for many different problems such as anemia, upper respiratory infections, blood pressure evaluations, rashes, follow-up on diabetes, vaginitis, emotional problems, allergy injections, and counseling about over-the-counter drugs. In all instances when the problems fell out of the expertise or scope of protocol of the FNP, the employees were referred to their own physicians or the sponsoring physician.

Based on fees from the Industrial Commission for the

State of North Carolina, the 800 possibly-job-related visits represented $16,000. Recognizing that many of the workers would not have sought medical care for their injuries, we used the actual claims costs to figure savings. The table below illustrates the claims experience during the three years under study:

Year	*Number of Claims*	*Cost*
1981	108	$33210
1982	58	34272
1983	47	25293

Assuming that without the FNP the worker's compensation claims for 1983 would have remained equal to the average of 1981 and 1982, or $33,741, this actual claims cost of $25,293 represents a savings of $8448. Besides the reduction in money spent on claims, there was also a reduction in the number of claims.

Using the fees for worker's compensation for health care counseling gives a total of $41,932.00. Estimating that only 50% of these employees would have sought medical help without the program brings the savings to $20,966.00.

Preventive maintenance represented a savings of $9,275.00 using a similar fee scale. Realizing that these savings would probably be real for the industry, the figures were not adjusted.

There were some interesting observations on insurance claims filed during the two fiscal years the program was in existence as illustrated in the table below.

Year	*Employee Claims*	*Dependent Claims*
1981	346	221
1982	332	234
1983	282	313

Fiscal year 1981 was the year prior to starting the program. The study period actually covered parts of fiscal year 1982 and 1983. In 1982 there was a reduction in employee claims by 4.2% compared with 1981, and a rise in dependent claims of 5.1% for the same time. In 1983 the employee claims dropped by 22.6% compared with 1981 while the dependent claims rose 29.4% compared with 1981. The reduction in employee claims enabled the industry to avoid a 12.5% insurance rate increase for 1983 and 1984, an estimated savings of $150,000. Other furniture manufacturers in the same community *did* have a 12.5% insurance increase annually during this period. The $150,000 figure is the value placed by the company auditors.

Absences in 1983 were 6968 fewer man-days than in 1981. At $48 per day ($6/hr) this represents a savings of $41,808 to the employees in lost wages. The savings to the company by the employees being on the job are not as easy

Table 1
Patient Visits to the FNP and Their Calculated Cost

	Patient Encounters				Costs		
	Audio	Job Related	Preventive Care	Health Care	Worker's Comp Fees	Preventive Care Costs	Health Care Costs
Hematology		0		16	20.00	0.00	320.00
ENT		0		452	20.00	0.00	9040.00
Eye		100		15	20.00	0.00	300.00
Respiratory		0		42	20.00	0.00	840.00
Cardiovascular		0		610	20.00	0.00	12200.00
Musculoskeletal		315		49	20.00	0.00	980.00
Skin		75		103	20.00	0.00	2060.00
Ob/Gyn				39	20.00	0.00	780.00
G/U		0		110	20.00	0.00	2200.00
Neurology		0		28	20.00	0.00	560.00
Endocrine		0		64	20.00	0.00	1280.00
Trauma		150		33	20.00	0.00	660.00
Counseling		150		158	20.00	0.00	3160.00
Gastrointestinal		0		78	20.00	0.00	1560.00
Complete physical		0	136	0	35.00	4760.00	0.00
Health check		0	45	0	20.00	900.00	0.00
Tetanus injection		0	96	0	6.00	576.00	0.00
Blood tests		0	225	0	9.00	2025.00	0.00
Urinalysis		0		184	8.00	0.00	1472.00
Hearing	450	0		0		0.00	0.00
Flu Immunization		0	169	0	6.00	1014.00	0.00
Throat culture		0		106	6.00	0.00	636.00
Dosimeter	20	0		0		0.00	0.00
Pelvic exam		0		19	20.00	0.00	380.00
Allergy injection		0		61	4.00	0.00	244.00
Weight check		0		28	20.00	0.00	560.00
Ear wash		0		18	20.00	0.00	360.00
OTC drugs		0		117	20.00	0.00	2340.00
Suture removal		8		0	20.00	0.00	0.00
Steristrip		2		0	20.00	0.00	0.00
Totals	470	800	671	2330		9275.00	41932.00

to measure.

The table below lists the savings to either the company or the employee with the Family Nurse Practitioner.

Audiometry	$3760
Worker's compensation	8448
Preventive care	9275
Health care counseling	20966
Loss in man days (6968)	41808
Savings in insurance premiums	$150000
Total	$234257

For a more accurate total of savings it is necessary to subtract the cost of the program from the above figure. During the year 1983 the total cost of the program was $28,109.50. This figure includes the salary for the FNP, materials and commercial lab fees. The expenses are low because the FNP worked only four hours per day for the first three months of 1983. The only other expenses for the program were the consulting fees of $2500 for the physician. The net savings are listed below:

Gross savings	$234257.00
Salary and other expenses	−28109.50
Consulting fees	−2500.00
Total	$203647.50

Discussion

The furniture manufacturer has another plant in Mississippi which did not use a FNP. The employee insurance claims there rose at a rate comparable to the dependent claims at the North Carolina plant. The worker's compensation claims in Mississippi did not show a drop as they did in our plant in North Carolina. The manufacturer used the out-of-state plant as a control to evaluate the value of the FNP.

The measurable savings alone justify the use of a FNP in the industrial setting. There are many unmeasurable savings in using a FNP. Employee morale improved in the plant using the FNP. While many of the employees seeing the FNP for health care counseling may not have visited physicians' offices or other health facilities, many would, requiring an absence from work of at least half of a day. Some of these savings are reflected in the decrease in absences.

The literature does not report any such previous use of a Family Nurse Practitioner, although we know of a few similar programs in North Carolina. McClure in a paper presented at the Greater New York AOHN alluded to this expanded role for the nurse, but did not report it being put into practice.[2] Traditional roles for the Family Nurse Practitioner have been screening, counseling, and referral.[3, 4] The net savings alone prove this is a viable technique for reducing industrial health care costs.

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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

January 7-March 1

Postgraduate Course in Medical Sonics
Place: Winston-Salem
Credit: 35 hours Category I AMA
Info: James F. Martin, M.D., Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 9

A Model for the Development of Gifted Children
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winston-Salem 27101-2482. 919/723-2482

January 13-16

Beyond Advanced Clinical Teaching Skills
Place: Rougemont
Credit: 20 hours Category I AMA and AAFP
Info: Dr. Katherine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

January 26

Sixth Annual Pulmonary Disease Update
Place: Greenville
Credit: 6 hours Category I AMA
Fee: $60.00
Info: Mary Valand, Box 7224, ECU School of Medicine, Greenville 27834. 919/758-5200

February 6

Grief Process in Children
Place: Winston-Salem
Info: Child Guidance Clinic, Inc., 1200 Glade Street, Winson-Salem 27101-2482. 919/723-2482

February 13

Anxiety Disorders
Place: Greenville
Fee: $30
Credit: 3.5 hours
Info: Mary Valand, Box 7224, ECU, Greenville 27834. 919/758-5200

OUT OF STATE

January 17-19

Advanced Ultrasound Seminar
Place: Orlando, FL
Credit: 14 hours Catetory I AMA
Info: James F. Martin, M.D., Bowman Gray, 300 South Hawthorne Road, Winston-Salem 27103. 919/748-4505

January 22

38th Annual Stoneburner Lecture Series: Rehabilitation Medicine
Place: Richmond, VA
Info: Kathy Martin, Box 48, MCV Station, Richmond, VA 23298. 804/786-0494

January 25-27

Winter Conference on Geriatrics
Place: Hot Springs, VA
Credit: 10 hours AAFP prescribed
Fee: $100
Info: NC Academy of Family Physicians, Box 20146, Raleigh 27619

January 26-31

Dermatology for Non-Dermatologists
Place: Cancun, Mexico
Info: Division of Dermatology, Box 3135, Duke University Medical Center, Durham 27710. 919/684-2504

January 27-February 2

Surgical Management of Malignant Disease
Place: Vail, CO
Credit: 25 hours Category 1 AMA
Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

February 3-8

Selected Topics in Internal Medicine
Place: Snowshoe, WV
Credit: 20 hours Category I AMA
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878

February 3-8

Sports Medicine for the Primary Care Physician
Place: Snowshoe, WV
Credit: 20 hours Category 1 AMA and AAFP
Info: Cindi Easterling, Box 3108, DUMC, Durham 27710. 919/684-6878

February 16-23

Radiology Postgraduate Course
Place: Ixtapa, Mexico
Credit: 25 hours Category I AMA
Info: Jackie Wright, Box 3834, DUMC, Durham 27710. 919/681-2711 ext. 285

Letters to the Editor

More on Thyroid Nodules

To the Editor:

No one questions that fine-needle aspiration (FNA) biopsy offers a safe, inexpensive adjunct to the diagnosis and management of thyroid nodules. However, controversy exists as to when to aspirate a thyroid nodule. A traditional approach might include thyroid ultrasonography (aspirate if cystic) and then radionuclide scintiscan (aspirate if hypofunctioning). Some endocrinologists use thyroid suppression alone to treat the non-cystic, hypofunctioning thyroid nodule in patients at low risk for cancer (e.g., female patients more than 25 years old). My approach to the solitary thyroid nodule has changed.[1] I perform a FNA biopsy when I first see the patient for two reasons.

1) FNA biopsy often provides a tissue diagnosis. An experienced cytopathologist trained in reading thyroid needle aspirates can frequently make a specific pathologic diagnosis. Scintiscan and ultrasonography cannot do this. This is not to say that FNA biopsy is always diagnostic. The nature of thyroid tissue itself does not always permit the cytopathologist to exclude thyroid carcinoma from benign adenoma. Of those patients with abnormal cytologic findings (suspicious for malignancy, probably malignant, or indeterminate), only 20% have malignancy at surgery.[2]

2) FNA biopsy costs less. For the dollars spent, FNA gives more information at a lower expense. At Duke, thyroid scintiscan ($159) and ultrasonography ($143) cost more than FNA biopsy ($91). Because most patients do not have high risk factors for thyroid carcinoma (single thyroid nodule in youth, history of irradiation, clinical signs of infiltration, hoarseness, etc.) and eventually have FNA biopsy anyway, many dollars and much time are saved by performing FNA biopsy at the outset. Furthermore, since about 20% of thyroid nodules are cystic, FNA diagnoses and treats the problem in this set of patients.

Although the FNA technique is a simple office procedure, best results come from physicians who have experience with FNA biopsy. Since thyroid masses are best palpated while the patient sits or stands, I ask the patient to sit in a chair while I stand behind to palpate and fix the nodule between my index and third fingers. With the thumb and index finger of my other hand, I hold a 21 gauge needle's hub which is attached to a syringe via a connecting tube. An assistant aspirates the obturator of the syringe.[3] I usually make three passes with the needle to insure adequate sampling. Any fluid is sent to cytopathology in a heparinized Vacutainer tube. If the aspirate is "dry," I use air to force the scant amount of material within the needle onto a slide, spread the aspirate evenly with the needle tip, fix the material in 70% ethanol or with a commercial spray fixative, and send the slide to the cytopathology lab for processing. If a cytopathologist is not available locally, specimens should be mailed to an appropriate center.

If the aspirate is suspicious or frankly malignant, I proceed to surgical extirpation. For the euthyroid patient whose FNA biopsy is not suspicious and whose risk factors are low (this group makes up more than 80% of all patients with thyroid nodules), I prescribe thyroid suppression with L-thyroxine. Contrary to what Dr. Werk and colleagues recommend,[4] I do not use doses of 0.2 and 0.3 mg/day of L-thyroxine since patients often become thyrotoxic with this amount of medication. Older people do not tolerate excessive thyroid suppression. Most persons are treated with 0.1 to 0.15 mg/day. An occasional obese patient may need 0.2 mg/day. Follow-up visits (6 weeks after initiation of L-thyroxine and 4-6 months thereafter) to check serum thyroxine level and size of the nodule are mandatory. In the rare patient with a functioning adenoma, thyroxine treatment may lead to hyperthyroidism. The scintiscan in these cases demonstrates increased activity over the nodule despite continued thyroid suppression. L-thyroxine is stopped and the patient is followed.

The euthyroid patient whose nodule regresses after a few months on L-thyroxine requires no studies other than yearly thyroxine levels. Sometimes the nodule (particularly if present for years prior to suppression) does not change in size. One can be sure that the doses of thyroxine are adequate if TRH causes no rise in the serum TSH or if the 24 hr thyroidal I-131 uptake is less than 5%; the former study appears to be more sensitive. A nodule which enlarges in spite of thyroid suppression is very suspicious of malignancy. However, a sudden increase in size suggests hemorrhage into the nodule and FNA confirms this. In the absence of hemorrhage, progressive enlargement of a thyroid nodule in a patient who is adequately suppressed calls for surgical intervention.

Is the initial performance of FNA biopsy an unusual method of approach for managing a solitary thyroid nodule? Because the Mayo Clinic has extensive experience with thyroid FNA (over 5000), I recently asked Hossein Gharib, M.D., a member of the thyroid group at the Mayo Clinic,[2] how they usually evaluated a thyroid nodule. FNA biopsy is their initial study in any patient with a thyroid nodule. Their observations as well as my own have reassured me that FNA biopsy is a safe, reasonable, and cost-effective first step in the diagnosis and management of the solitary thyroid nodule.

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To the Editor:

The percentage cancer index computed by Werk et al. in the October issue of the NCMJ points up the low specificity of ultrasound and scintiscan in detecting benign thyroid nodules. Although these procedures detect nearly all malignant nodules, 80 to 90 percent of positive tests will have no malignancy.[1] The specificity of these procedures is 10 to 20 percent. The specificity of thyroid hormone suppression, defined as growth or unchanged while taking thyroid hormone, is 30 to 40 percent.[1] This means that the majority of benign nodules do not shrink in size with thyroid hormone suppression. Fine needle aspiration biopsy has a specificity of 70 to 80 percent.[2, 3] Again, specificity relates to the percentage of benign thyroid nodules diagnosed by the procedure. These reports come from medical centers where a thyroidologist takes the medical history, examines the patient, performs the aspiration and interprets the cytological specimen. These reported figures are highly biased when applied to smaller medical communities.

The primary limitation of fine needle aspiration is in the overlap of cytological characteristics of benign and malignant follicular neoplasms. Hence, all follicular neoplasms should have a large needle or cutting needle biopsy for tissue morphology. The other option is to refer all follicular neoplasms for surgical excision, but this reduces the specificity since follicular adenoma is more common than follicular carcinoma. Another problem in interpretation relates to the pleomorphic changes in follicular cells caused by cytotoxic antibodies in autoimmune thyroiditis. If the sample misses the lymphocytic infiltrate, the diagnosis will often be reported as suspicious for carcinoma. The initial thyroid profile should include thyroid antibodies, the presence of which will sway the interpretation.

The clinician who infrequently evaluates thyroid nodules needs all the diagnostic help available before arriving at a recommendation for surgical excision. An approach that has been successful for me over the past few years utilizes ultrasound, scintiscan and fine needle aspiration (FNA) biopsy (figure 1). Since cystic and hyperfunctioning nodules account for 30 percent of all solitary thyroid nodules and are rarely malignant, it is reasonable to begin with ultrasound and scintiscan. Ultrasound should precede scintiscan since cystic nodules will be nonfunctional on scintiscan, obviating the need for the latter procedure. All suspicious aspirations should be followed by large needle or cutting needle biopsy. This approach has yielded a percentage cancer index of approximately 50 percent, although admittedly I have gained proficiency in cytological interpretation. Just as importantly, 75 percent of patients are spared a surgical excision procedure.

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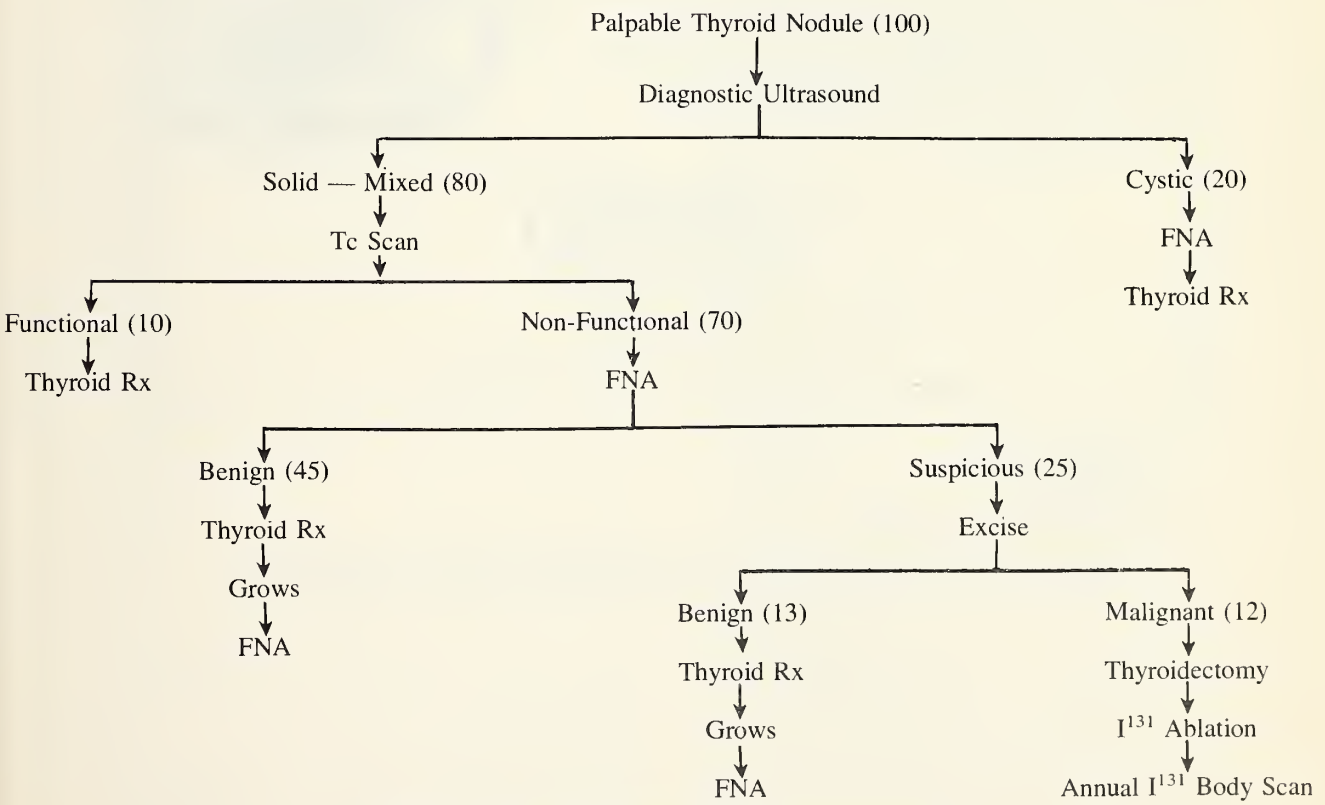
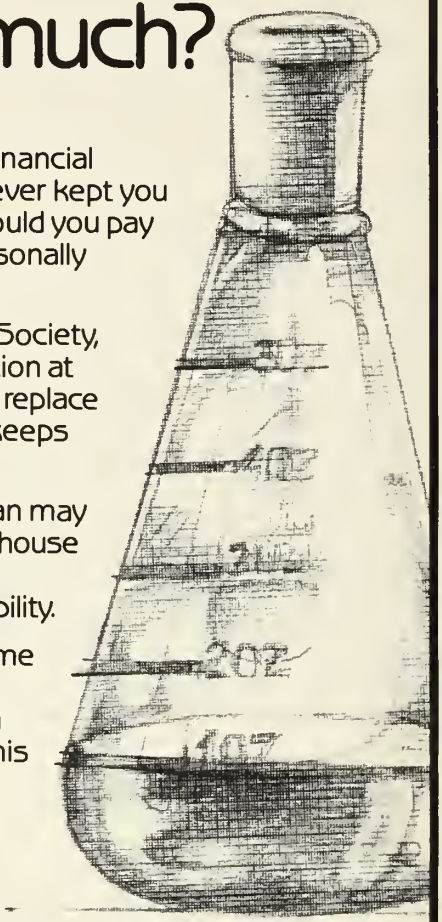


Figure 1. Algorithm for Evaluation of a Thyroid Nodule.

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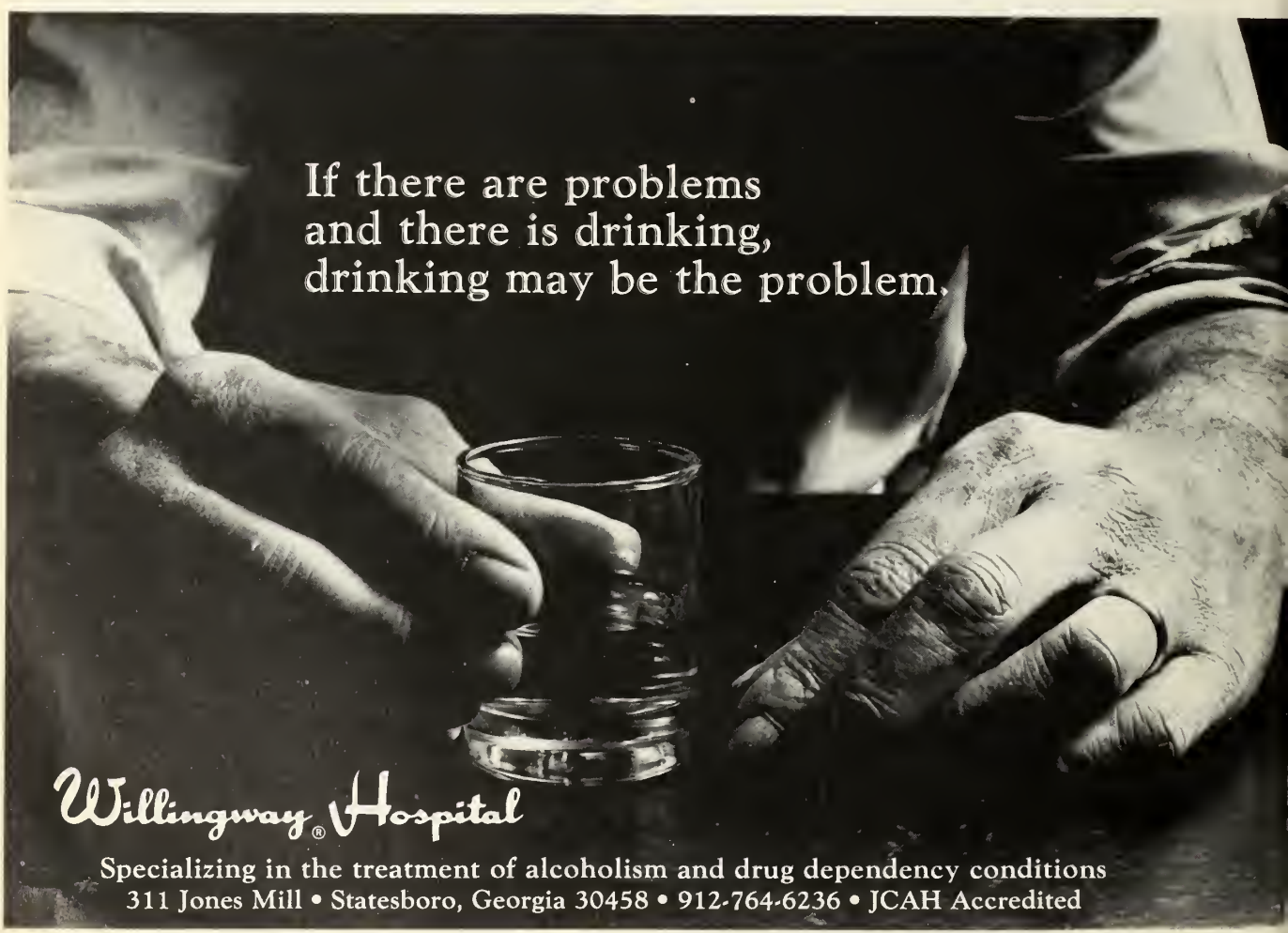
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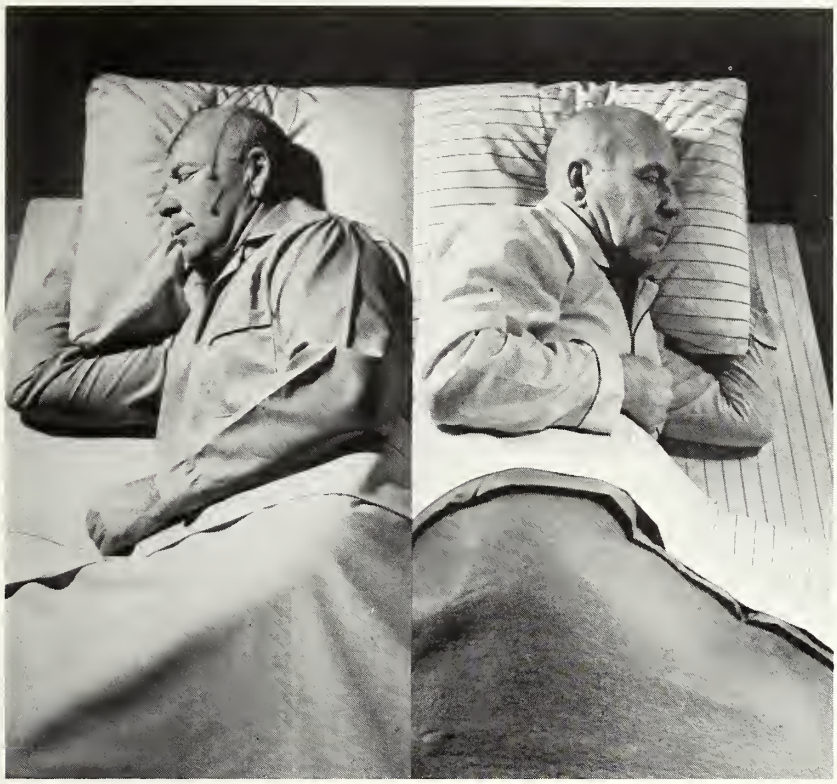
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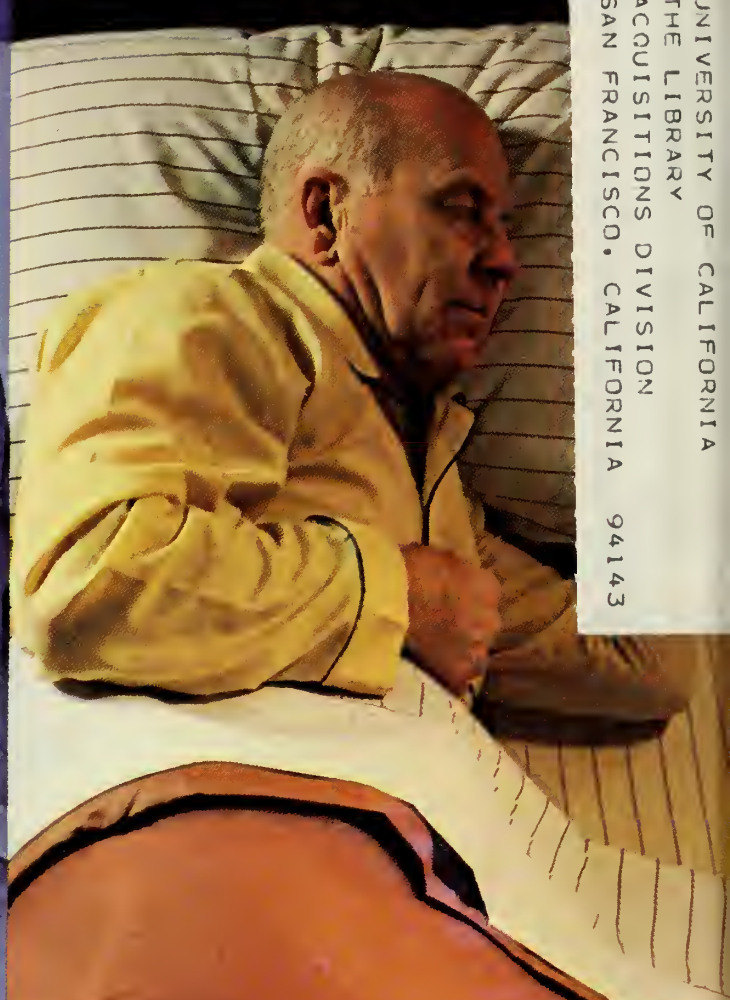
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